EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Protelos and Osseor

Strontium ranelate

Procedure no. EMEA/H/C/560/PSU/031 and EMEA/H/C/561/PSU/031

Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisations

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Protelos and Osseor, the scientific conclusions of PRAC are as follows:

Data submitted in the present PSUR raise concern regarding cardiovascular safety beyond the already recognized risk for venous thromboembolism. An increased risk for serious cardiac disorders, including myocardial infarction has now been identified. This conclusion is predominantly based on data from pooled placebo-controlled studies in post-menopausal osteoporotic patients (3,803 patients treated with strontium ranelate, corresponding to 11,270 patient years of treatment, and 3,769 patients treated with placebo, corresponding to 11,250 patient years of treatment). In this data set, a significant increase of serious cardiac disorders (6.9% versus 5.7% OR 1.22 [1.02 ; 1.46]) and of myocardial infarction (1.7% versus 1.1 %), with a relative risk of 1.6 (95% CI = [1.07 ; 2.38]), has been observed in strontium ranelate treated patients compared with placebo treated patients. Further, there was an imbalance of such events both in a study in osteoporotic men and in a study in osteoarthritis. In addition, there is a possible mechanistic rationale for an increased risk for serious cardiac disorder including myocardial infarction.

Taking all currently available efficacy and safety data, including the newly identified risk for serious cardiac disorders, presented within this PSUR procedure into account, the PRAC recommends to introduce risk minimization measures to reduce the target population by excluding patients with high risk for ischemic cardiac disorders, and to restrict the indication to the patients who are most likely to benefit from the treatment i.e. women with severe osteoporosis and at high risk of fracture and men with severe osteoporosis at increased risk of fracture. The PRAC considers that the introduction of these measures taken together with further steps as outlined below allows the identification of a patient population for which the benefit/risk remains favorable.

These additional measures include the following:

The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks. In addition, the PRAC recommends that the product should not be used in patients with established, current or history, of ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and/or uncontrolled hypertension. Moreover, patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration.

Furthermore, the PRAC recommends that the product should only be prescribed by physicians with experience in the treatment of osteoporosis and that before starting treatment and thereafter at regular intervals, patients should be evaluated with respect to risk of developing cardiovascular disease.

In addition, the PRAC recommends that the prescribers are informed of these changes to the product information via a Direct Healthcare Professional Communication (DHPC).

The MAH should also perform a study to evaluate the compliance with the new prescribing recommendations.

Given the overall safety profile, characterized by various serious risks including venous thromboembolism, cardiac disorders and skin reactions; and particularly given the need for a study that will evaluate the compliance with the new prescribing information, the product should be subject to additional monitoring.

The next PSUR should cover the period from 22 September 2012 to 21 September 2013 and be submitted within 70 days of the data lock point.

The risk management plan (RMP) should be revised to include serious cardiac disorders including myocardial infarction as an important identified risk. The non-interventional safety study should be added to the Pharmacovigilance Plan, including time lines for submission of a protocol and a final study report. The DHPC should be added among risk minimization measures. Furthermore, all relevant sections of the RMP should be revised to reflect this new important identified risk.

The PRAC concluded that, on the basis of the current assessment, the benefit/risk balance of strontium ranelate remains favourable in the identified restricted population. However, the PRAC considers that, in view of the newly identified risk of serious cardiac disorders including myocardial infarction, and in order to allow all available data on efficacy and safety to be taken into account, the benefit/risk balance of medicinal products containing strontium ranelate should be further evaluated in an expedited timeframe.

Recommendations

Based on the PRAC review of data on safety and efficacy submitted during this PSUR procedure, the PRAC considers by majority decision that the risk-benefit balance of medicinal products containing the active substance strontium ranelate remains favourable but recommends that the terms of the marketing authorisations should be varied as follows:

Update of section 4.1 of the SmPC to restrict the indication to patients with severe osteoporosis, and in postmenopausal women, at high risk of fractures. In section 4.1, it is also reminded that the decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks. Update of section 4.3 of the SmPC to contraindicate the use of strontium ranelate in patients with established, current of history of, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and / or uncontrolled hypertension. In addition, update of sections 4.2, 4.4 and 4.8 of the SmPC to establish that the treatment should only be initiated by a physician with experience in the treatment of osteoporosis, to add a warning on cardiac ischaemic events and to add myocardial infarction as a common adverse reaction.

The Package leaflet is updated accordingly.

In addition, the PRAC recommends the following changes to the conditions of the MA:

- Conditions regarding the supply and use: restricted medical prescription.

- Obligation to conduct post-authorisation measures: study to assess the effectiveness of the agreed risk minimisation measures.

The amendments recommended to be introduced to the product information and conditions to the marketing authorisation are detailed in Annex 1 and Annex 2.

In addition the PRAC recommends that the prescribers are informed of these changes to the product information via a Dear Healthcare Provider Communication (DHPC).

Further the PRAC recommends that the product should be subject to additional monitoring.

The PRAC also recommends that in view of the newly identified risk of serious cardiac disorders including myocardial infarction, and in order to allow all available data on efficacy and safety to be taken into account, the benefit/risk balance of medicinal products containing strontium ranelate should be further evaluated in an expedited timeframe.

In addition, the MAH should also address the following issues in the next PSUR:

- An increase in serious unlisted events in PSUR 12 should be followed up and the MAH is requested to present a summary table, including the findings in the PSUR 13 period.

In addition, the MAH should submit an updated RMP within the next relevant procedure in order to address the following issues:

- The RMP should be updated to reflect the conclusions of the PRAC after the evaluation of the PSUR.
- Six signals previously categorized as potential risk were considered as false signals and closed. However, the PRAC considers that "interstitial nephritis, "depression", "bone sarcoma" and "pancreatitis" should remain in the potential risk list.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisations

On the basis of the scientific conclusions for Protelos and Osseor the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing the active substance strontium ranelate is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisations should be varied.

APPENDIX

Divergent Position

The undersigned members of PRAC did not agree with the CHMP's opinion recommending that the Marketing Authorisation should remain for Protelos/Osseor.

The reasons for divergent opinion were as follows:

The benefit risk balance is considered to be unfavorable in the now proposed restricted indication due to the following:

- It can be estimated from the compiled data provided from randomized placebo-controlled studies that preventing one non-vertebral fracture (including fractures not requiring surgery) with strontium ranelate treatment in post-menopausal women roughly corresponds to the risk of causing one serious cardiac disorder or a venous thromboembolic event. In addition, strontium ranelate treatment is associated with rare but serious adverse events such as serious skin reactions. The prevention of usually asymptomatic radiological vertebral fractures or non-vertebral fractures not requiring surgery is considered to have a lower clinical importance compared to these serious adverse events.
- There is considerable uncertainty regarding the evidence of benefit in support of the newly proposed indication in severe osteoporosis. Furthermore the proposed risk minimization measures are not expected to sufficiently well reduce the risk for myocardial infarction, VTE and serious cardiac disorders. Risk factors for these undesirable effects are partly overlapping with risk factors for osteoporosis.

Considering these aspects we, the undersigned, believe a suspension of the marketing authorisation would be appropriate in the current situation while further data in support for a positive benefit risk balance in a restricted population is gathered.

London, 25 April 2013

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