EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)
Pharmacovigilance Risk Assessment Committee (PRAC)

Protelos and Osseor

Strontium renalate

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

Applicant/Marketing authorisation holder: Les Laboratoires Servier

CHMP scientific conclusions and PRAC Assessment report of the Review under Article 20 of Regulation (EC) No 726/2004

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1. Scientific conclusions and CHMP's detailed explanation on the scientific grounds for the differences with the PRAC recommendation

Note

Scientific conclusions as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Scientific conclusions

Overall summary of the scientific evaluation of Protelos/Osseor by the PRAC

Background information

In the European Union there are two centrally authorised products containing strontium ranelate: Protelos and Osseor, both authorised in September 2004.

Strontium ranelate, the active substance of Protelos/Osseor, is composed of two atoms of stable strontium and one molecule of ranelic acid. Strontium ranelate dissociates at the gastrointestinal level. Strontium is a cation chemically and physiologically closely related to calcium. Ranelic acid is an organic, highly polar molecule without pharmacological activity. It is suggested that strontium acts through dual mechanisms of inhibition of resorption by osteoclasts and maintenance or stimulation of bone formation by osteoblasts.

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, was assessed by the PRAC and raised concerns regarding cardiovascular safety beyond the already recognised risk for venous thromboembolism.

As a result of the PRAC assessment, an increased risk for serious cardiac disorders (including myocardial infarction) was identified and risk minimisation measures specifically targeting the identified risk were recommended in April 2013. The risk minimisation measures included 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 treatment.

Following the introduction of the above risk minimisation measures, further in-depth evaluation of the benefits and risks of products containing strontium ranelate was considered necessary and the current procedure under Article 20 of Regulation (EC) No 726/2004 was initiated.

Scientific discussion

The postmenopausal osteoporotic (PMO) population for strontium ranelate comprises data from 7 randomised studies: 2 phase II studies CL2-004 (Meunier, 2002; NP07869) and CL2-005 (Reginster 2002; NP08511) and 5 phase III studies CL3-009 (Meunier, 2004; NP08338/NP22819), CL3-010 (Reginster 2005; NP08340/NP22824), CL3-013 (Hwang 2008; NP22514), CL3-015 (Liu 2009; NP25026), CL3-017 (NP24357). This set consisted of 7572 patients (3803 patients treated with strontium ranelate vs 3769 patients treated with placebo).

In order to assess the impact of the restrictions introduced in the product information, namely the restriction to patients with severe osteoporosis and patients without the contraindications (current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism; temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest; established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or uncontrolled hypertension), post-hoc subgroup analyses of the existing clinical trial data were performed.

Regardless of the definition of severity of osteoporosis used, the estimates of cardiac and thromboembolic risks change in the restricted population (excluding those with contraindications) when compared to the whole PMO population dataset. However, there are uncertainties regarding statistical

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power given the restricted sample size and the event rate, and therefore around the reassurance provided by these subgroup analyses.

In addition, the PRAC expressed serious concerns about whether the contraindications and warnings implemented to mitigate cardiac and thromboembolic risks could be achievable in clinical practice, considering that strontium ranelate is intended for long-term treatment of a population of elderly patients whose cardiovascular status may deteriorate over time.

In addition, the PRAC considered all the other risks associated with strontium ranelate (which include serious skin reactions (including DRESS syndrome, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders). All of these risks can be serious and cause significant problems in daily life, particularly considering a target population of elderly patients on long-term treatment.

An Ad-Hoc expert group composed of experts from different areas including osteoporosis, cardiology, epidemiology and general practice was convened to provide advice to the PRAC. In view of the data provided and other treatment alternatives available, some experts, in particular the experts in osteoporosis were of the opinion that a patient population could benefit from the product. However, the experts considered that, if available, strontium ranelate should only be prescribed as second line treatment in patients with severe osteoporosis as defined by the WHO, and who do not tolerate other alternative treatments. Experts also specified that strontium ranelate should be used only in severe osteoporosis with significant fragility fracture such as hip and not "trivial" ones such as metacarpal (which was given as an example).

Radiological vertebral fractures are a common finding in postmenopausal women and are usually asymptomatic. A typical symptomatic vertebral fracture causes acute pain and decreased mobility that lasts about one month. Fractures that require surgery are the most dangerous aspect of osteoporosis. Hip fracture and the following surgery, in particular, are associated with risks such as permanent disability and increased mortality.

Based on the overall fracture data from randomised, placebo-controlled studies in postmenopausal women, strontium ranelate is found to have only a modest benefit in the reduction of fractures, particularly the most serious types of fractures. In the PMO population, the reduction of non-vertebral fractures in strontium ranelate patients compared to placebo was 5 events per 1000 PY, and new vertebral fractures 15 events per 1000 PY. The reduction in hip fractures was approximately 0.4 events per 1000 PY (non-significant).

For this review, new subgroup analyses were conducted in the data from clinical trials to explore whether the modest benefit identified in the PMO population is maintained in the currently approved population of patients. These analyses have limitations due to their unplanned nature and low numbers, however the PRAC considered that the results raise questions on whether the effect size observed in the whole PMO population is even maintained in the restricted population.

Overall conclusion

Having considered the overall submitted data provided by the MAH in writing and in the oral explanation, the PRAC concluded that:

Strontium ranelate is associated with a number of serious risks; namely serious cardiac disorders (including myocardial infarction), thromboembolic events (including VTE), serious skin reactions (including DRESS syndrome, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders. For the cardiac and

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thromboembolic events, frequencies have been calculated based on data from controlled clinical studies. In these studies, a statistically significant increase of serious cardiac disorders of 4 events per 1000 PY was observed for the strontium ranelate treated group compared with placebo. Among those, myocardial infarction corresponded to 2 additional events per 1000 PY. The number of additional thromboembolic events associated with strontium ranelate treatment was also 4 per 1000 PY. Among these, VTE corresponded to 2 additional events per 1000 PY.

The MAH provided a set of retrospective subgroup analyses of the PMO studies, to consider the impact of excluding patients with contraindications relating to cardiovascular and thromboembolic risks according to the current product information. The exclusion of such patients impacted on the statistical significance of the observed increased risks. However, there is uncertainty regarding the statistical power of the subgroup analyses considering the restricted sample size and the event rate, and therefore around the reassurance provided by these subgroup analyses.

There are serious concerns about whether the contraindications and warnings implemented to mitigate cardiac and thromboembolic risks could be achievable in clinical practice, considering that strontium ranelate is intended for long-term treatment of a population of elderly patients whose cardiovascular status may deteriorate over time.

When fracture data from randomised, placebo-controlled studies in postmenopausal women were reviewed, the magnitude of the benefit of fracture prevention was found to be modest, particularly regarding the most serious types of fractures. The reduction of non-vertebral fractures in strontium ranelate treated patients compared to placebo was 5 events per 1000 PY and new vertebral fracture 15 events per 1000 PY. The reduction in non-vertebral fractures consisted mainly of fractures in ribs-sternum, pelvic-sacrum and humerus. The observed reduction for hip fractures was approximately 0.4 per 1000 PY (non-significant). The new subgroup analyses presented raise questions on whether the effect size observed in the whole PMO population is maintained in the restricted population.

The PRAC concluded that when the identified serious risks, for which there are considerable doubts that they can be adequately mitigated during long-term treatment, are considered in the context of the modest benefit shown in terms of fracture prevention, the benefit/risk balance of strontium ranelate is considered to be not favourable.

The PRAC therefore recommended the suspension of the marketing authorisations for Protelos and Osseor and considered that, in order for the suspension to be lifted, additional robust data that enables the identification of a patient population in whom benefits outweigh the risks is needed.

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Grounds for PRAC recommendation

Whereas

- The Committee considered Protelos and Osseor (strontium ranelate) in the procedure under Article 20 of Regulation (EC) No 726/2004, initiated by the European Commission.
- The Committee reviewed all data available on the safety and efficacy of strontium ranelate, including retrospective subgroup analyses on the postmenopausal women clinical trial dataset to consider the impact of the restrictions recently introduced on the safety of patients and on the effect size observed.
- The Committee took note of a number of risks associated to strontium ranelate, namely serious cardiac disorders (including myocardial infarction), thromboembolic events (including VTE), serious skin reactions (including DRESS syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders.
- The Committee considered that the exclusion of patients with contraindications relating to cardiovascular and thromboembolic risks impacted on the statistical significance of the observed increased risks. However, there is uncertainty regarding the statistical power of the subgroup analyses considering the restricted sample size and the event rate, and around the reassurance provided by these analyses.
- The Committee also considered that there are serious concerns on whether the contraindications and warnings implemented to mitigate cardiac and thromboembolic risks could be achievable in clinical practice, considering that Protelos and Osseor are intended for long-term treatment of a population of elderly patients whose cardiovascular status may deteriorate over time.
- The Committee considered that, when the fracture data from randomised, placebo-controlled studies in postmenopausal women are reviewed, the magnitude of the benefit in fracture prevention was found to be modest particularly for the most serious types of fractures. The retrospective subgroup analyses raise questions on whether the effect seen in the postmenopausal population is maintained in the restricted population.
- The Committee concluded, in view of the available data, that given the number of identified serious risks, for which there are considerable doubts that they can be adequately mitigated during long-term treatment, in the context of the modest benefit shown in terms of fracture prevention, the benefit-risk balance of Protelos and Osseor is not favourable.

The PRAC, having considered the matter, recommended the suspension of the marketing authorisation for Protelos and Osseor.

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CHMP detailed explanation of the scientific grounds for the differences with the PRAC recommendation

The CHMP considered the PRAC recommendation and the additional information provided by the MAH both in writing and at an oral explanation.

Points of differences with the PRAC recommendation and scientific rationale of the CHMP position

Evaluation of newly identified risks and measures proposed to minimise these risks

The CHMP agreed with the conclusions of the PRAC that the use of strontium ranelate in a broad osteoporosis population (postmenopausal population) is associated with a number of serious risks; namely serious cardiac disorders (including myocardial infarction), thromboembolic events (including VTE), serious skin reactions (including DRESS syndrome, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders.

For the cardiac and thromboembolic events, frequencies have been calculated based on data from controlled clinical studies. In the pooled clinical trial population of postmenopausal women (PMO patients dataset, n=7572) encompassing 3803 patients treated with strontium ranelate (11270 patient years) the odds ratio [95%CI] for myocardial infarction (MI) in strontium ranelate treated versus placebo treated patients was 1.60 [1.07; 2.38], p=0.020. The CHMP noted that cardiovascular (CV) mortality and overall mortality were not increased in the strontium ranelate group versus the placebo group. The follow-up period in clinical studies after occurrence of an AE such as MI was limited to 30 days but would appear to cover early fatalities due to MI.

The MAH provided a set of retrospective subgroup analyses of the postmenopausal population studies, to consider the impact of excluding patients with contraindications relating to cardiovascular and thromboembolic risks according to the current product information. The CHMP agreed with the PRAC's conclusion that such retrospective subgroup analyses are associated with substantial uncertainties. However, the analyses of cardiovascular risk in a restricted population of patients without contraindications (n=4040) show an odds ratio [95%CI] for MI in the strontium ranelate group versus placebo of 0.99 [0.48; 2.04], p=0.988. Similarly, the risk for serious cardiac events was reduced in the subgroup of patients without contraindications (from 1.22, 95%CI [1.02-1.48]; p = 0.034 to 1.13, 95%CI [0.82-1.57]; p = 0.443), the difference versus placebo being no longer statistically significant.

Looking at the shift in point estimates across various analyses (whichever definition of severity of osteoporosis used), there was a clear tendency towards neutralisation of the cardiovascular risk in the patient population without contraindications. This indicates that the introduction of these contraindications was successful in minimizing the risks observed in the overall population of post-menopausal women. However, it has to be recognised that the informative value of these subgroup analyses is limited due to their post-hoc nature and small sample size and any statistical inferences drawn on subpopulations with and without cardiovascular risk factors that are derived from the overall patient population need to be interpreted with caution. From a methodological perspective, a definite conclusion on this matter would require the analysis of a different dataset.

Three epidemiological studies (DSRU, CLE-12911-021, CPRD study) performed in observational settings with different design and methodologies were taken into account by the CHMP in the current risk evaluation. The studies were well conducted, fairly large and had a reasonable length of follow up. Study CLE-12911-021, for example, was an observational international prospective cohort survey (non-interventional) performed in seven EU countries with the main objective to follow-up during 3

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years a cohort of post-menopausal women treated with strontium ranelate with a special focus on all potential safety concerns. The safety data set consisted of 12 076 patients with a mean follow-up time of 32.0 ± 9.7 months [24 956 patient-years (PY)]. It is acknowledged that these studies had limitations such as a relatively low number of strontium ranelate patients and low exposure in the CPRD study or lack of comparators (cohort study, DSRU), but none of these studies provided evidence of an increased risk of myocardial infarction with strontium ranelate.

The PRAC expressed serious concerns on whether the contraindications and warnings implemented to mitigate cardiac and thromboembolic risks could be achievable in clinical practice, considering that strontium ranelate is intended for long-term treatment of a population of elderly patients whose cardiovascular status may deteriorate over time. The CHMP acknowledges that this is challenging. However the CHMP took the view that assessment of cardiovascular risk is a primary task for practising physicians, mainly relying on accessible information (such as family and patient history, smoking status, body mass index, waist circumference, blood pressure) and commonly investigated laboratory values (such as blood glucose and lipids). This is required for many treatment decisions in older patients with comorbidities and physicians are familiar with addressing these aspects when taking a benefit-risk decision for each individual patient.

In order to address the concern that cardiovascular risk may increase considerably over time in the predominantly elderly target population, the MAH proposed regular assessment of the patients' cardiovascular risk. Repeated risk assessment is challenging, but should nonetheless be feasible within normal clinical practice. In order to support this activity, educational material including a prescribers' checklist and a patient alert card will be implemented.

The view that the risk may be manageable in clinical practice was also expressed by the majority of the members of the ad hoc expert group convened by the PRAC to discuss strontium ranelate. The experts also considered that there is a group of patients with severe osteoporosis as defined by the WHO, who do not tolerate alternative treatments and who could benefit from strontium ranelate.

The MAH has provided a study outline for a post-authorisation safety study using the EU-ADR Alliance databases. The study is designed to compare the incidence rates of cardiac and thromboembolic events in patients treated with strontium ranelate and with other treatments as well as the prevalence of contraindications in patients taking strontium ranelate before and after the sending out of the Direct Healthcare Professionals Communication (DHPC) in 2013 explaining the risk minimisation measures introduced at the time. This is expected to better characterise the risk in the restricted population and also to assess the effectiveness of the risk minimisation measures. The CHMP considered that the proposed study outline appears to address these issues and supported the strategy proposed.

In addition, other relevant changes have been implemented in the product information of strontium ranelate, strengthening the contraindications and warnings as well as restricting the indication for strontium ranelate to patients at high risk of fracture for whom treatment with other medicinal products is not possible due to, for example, contraindications or intolerance. Together with the comprehensive risk communication and the educational material consisting of a new DHPC, prescribers' checklists and patient alert cards, it can be reasonably assumed that such prominent restrictions of use will accordingly raise the awareness of both physicians and patients for a cautious exposure to this medicinal product.

Benefits of strontium ranelate in the treatment of osteoporosis

While it is agreed that the pooled postmenopausal dataset is relevant for safety evaluation, the CHMP considered that the anti-fracture efficacy should be analysed based on data from the phase 3 studies TROPOS and SOTI conducted over 3 years in a population at high risk of fractures, with fractures defined as primary endpoint. The inclusion of data from small phase II and III studies in a lower risk

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population and study duration of 1-2 years (with bone mineral density as the primary endpoint) may have diluted the anti-fracture efficacy of strontium ranelate. Efficacy in the reduction of vertebral fractures was clearly shown in the pivotal SOTI study (n=1640), with a relative risk reduction of -41% over 3 years. The magnitude of this effect is similar to that of bisphosphonates.

Hip fractures were not specifically studied in the phase III program, as it was not specifically requested in the relevant guidelines at the time of study planning; the primary endpoint in the TROPOS study was the incidence of new peripheral (non-spinal) osteoporotic fractures. The relative risk reduction of proximal femur and hip area fractures with strontium ranelate over 3 years (FAS population from TROPOS) was not statistically significant compared with placebo: 15% (RR=0.85, 95% CI [0.61; 1.19], p=0.333) and 21% (RR=0.79, 95% CI [0.59; 1.06], p=0.112), respectively.

The potential for reduction in the incidence of hip fractures was derived from post-hoc subgroup analyses of patients at high risk of hip fracture (age greater than or equal to 74 years and femoral neck T-score less than or equal to -2.4) in the TROPOS study corresponding to a difference of 7.3 events per 1000 PY; RR 0.64, 95% CI [0.41; 1.00], p=0.046. It has to be noted that there was a plausible rationale for the selection of this subgroup. Additional analyses in even smaller subgroups of patients (with different levels of osteoporosis severity and different risk for cardiovascular events) were presented by the MAH during this article 20 referral procedure, as requested by the PRAC. However, due to the limited sample size these estimations are associated with considerable uncertainty and are not considered to reliably reflect the size of the expected reduction in hip fracture incidence. No important new data have become available since approval of the product for reduction of the incidence of hip fractures based on analyses of the TROPOS study and hence there is no basis for questioning this efficacy claim. Moreover, for some of the other products authorised for treatment of osteoporosis the evidence for efficacy in hip fracture prevention is quite comparable to the one demonstrated for strontium ranelate.

Benefit-risk balance, with the newly agreed risk minimisation measures

Strontium ranelate is associated with a number of serious adverse events including serious cardiac disorders, thromboembolic events, serious skin reactions, disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders. In line with the concerns expressed by the PRAC, the CHMP concluded that the benefit/risk balance of strontium ranelate needed to be re-evaluated and measures taken in order to minimize those risks so that the benefit in a newly defined target patient population could outweigh the risks.

The CHMP took into consideration that there is a need for alternative treatments in osteoporosis, as it is known from the literature that a significant proportion of patients discontinue treatment with bisphosphonates (i.e. the most commonly used drugs) within the first year, while other patients may have contraindications or intolerability to other anti-osteoporotic drugs.

Strontium ranelate has a different mechanism of action from other available products; this might be a valuable alternative, particularly in long-term treatment of osteoporosis and for patients for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.

As far as vertebral fractures are concerned, strontium ranelate has comparable anti-fracture efficacy as bisphosphonates. Avoiding vertebral fractures is an important treatment goal as they are associated with high morbidity and mortality, substantially impact on the quality of life and are known to predict future fractures.

The CHMP agrees that the benefits of strontium ranelate are not considered to outweigh the potential adverse reactions in a broad osteoporosis population. However, the retrospective subgroup analyses

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performed by the MAH support the conclusion that the risks for vascular complications seemed to be reduced to a neutral level by the exclusion of patients with identified increased cardiovascular risk while anti-fracture efficacy seems to be preserved, even in the subset of patients with severe osteoporosis.

Having considered all of these issues, the PRAC recommendation and the oral explanation with the MAH at the CHMP plenary meeting, the Committee decided to raise further questions to the MAH, requesting an in-depth discussion and proposals for appropriate risk minimisation measures in order to mitigate the above mentioned risks of strontium ranelate. Having assessed the proposals put forward by the MAH in response to these questions, the CHMP concluded that the remaining issues are sufficiently addressed, and the proposed product information, educational material and post-authorisation safety study are endorsed. Consequently, the CHMP considered that the benefit-risk balance of strontium ranelate is positive in a restricted target population provided that the proposed measures are successfully implemented.

The implementation of these risk minimisation measures will be evaluated on a regular basis both within the incoming Periodic Safety Update Reports and by the results of the imposed PASS. The Risk Management Plan shall be updated to include all of the measures agreed.

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Grounds for differences with the PRAC recommendation

Whereas

- The CHMP took into account the PRAC recommendation and all the information provided by the MAH in writing and at an oral explanation.
- The CHMP agreed that there are a number of risks associated to strontium ranelate, including an increased risk of serious cardiac disorders observed in the postmenopausal population.
- The CHMP agreed that the retrospective subgroup analyses presented are associated with uncertainty. However, the CHMP considered that these show a clear tendency towards neutralisation of the cardiovascular risk when the population is restricted to patients with severe osteoporosis without contraindications. This is indicative that the risk minimisation measures previously put in place are successful in minimising the cardiovascular risk identified in the postmenopausal population.
- The CHMP agreed that implementation of all the proposed risk minimisation measures is challenging. Repeated risk assessment was nonetheless considered to be feasible within normal clinical practice, as expressed by the majority of the members of the ad hoc expert group meeting convened to discuss strontium ranelate.
- Given the totality of the risks associated to strontium ranelate, the CHMP considered it appropriate that use of strontium ranelate be restricted to patients for whom treatment with other medicinal products is not possible due to, for example, contraindications or intolerance.
- The CHMP requested that the MAH shall conduct a post-authorisation safety study to assess whether, within the limited patient population which is expected to be exposed to strontium ranelate, there is compliance with the restrictions introduced, and to collect further information on the risks of the medicinal product and on the effectiveness of the risk minimisation measures.
- While it is agreed that the pooled postmenopausal dataset is relevant for the safety evaluation, the CHMP considered that the anti-fracture efficacy should be analysed based on data from the clinical studies in which fractures were defined as a primary endpoint. In this respect, the magnitude of the benefit of strontium ranelate in the fracture prevention is considered unchanged.

The CHMP, having considered the PRAC recommendation dated January 2014 and the totality of the information provided by the MAH, is of the opinion that the benefit-risk balance of strontium ranelate remains positive in the restricted population, taking into account the agreed risk minimisation measures, including changes to the product information and additional pharmacovigilance activities.

The CHMP therefore recommended the variation of the marketing authorisations for Protelos and Osseor.

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Divergent positions to the CHMP opinion

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Divergent statement

We, the undersigned, find the benefit risk balance for strontium ranelate negative in the proposed indications. We are not convinced that the proposed risk minimisation measures are realistic and therefore they cannot achieve what is intended.

CHMP members expressing a divergent opinion:

Ondrej Slanar (CZ)	20 February 2014	Signature: .....
Pierre Demolis (FR)	20 February 2014	Signature: .....
Ivana Mikačić (HR)	20 February 2014	Signature: .....
David Lyons (IE)	20 February 2014	Signature: .....
Daniela Melchiorri (IT)	20 February 2014	Signature: .....
Nela Vilceanu (RO)	20 February 2014	Signature: .....
Kristina Dunder (SE)	20 February 2014	Signature: .....
Jan Mazag (SK)	20 February 2014	Signature: .....
Reynir Arngrímsson (IS)	20 February 2014	Signature: .....
Ingunn Hagen Westgaard (NO)	20 February 2014	Signature: .....

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2. PRAC Assessment report

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted, to be read in conjunction with subsequent CHMP scientific conclusions.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09 January 2014
EMA/112925/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Protelos and Osseor

Review under Article 20 of Regulation (EC) No 726/2004,

International non-proprietary name: strontium ranelate

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

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3. Background information on the procedure

In the European Union there are two centrally authorised products containing strontium ranelate: Protelos and Osseor, both authorised in September 2004.

A review under Article 20 was previously carried out for Protelos with a focus on venous thromboembolism (VTE) and serious skin reactions. The review was finalised in 2012 resulting in the addition of new warnings (patients over 80 years of age at risk of VTE) and contraindications (previous VTE, immobilisation) to the product information.

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, raised concerns regarding cardiovascular safety beyond the already recognised risk for venous thromboembolism.

As a result of the PRAC assessment, an increased risk for serious cardiac disorders (including myocardial infarction) was identified and risk minimisation measures specifically targeting the identified risk were recommended in April 2013. The risk minimisation measures included 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 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 agreed with the PRAC's recommendation for a further in-depth 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 Agency to assess the above concerns and their impact on the benefit- risk balance for the centrally authorised medicinal products Protelos and Osseor. The EC requested the Agency to give its opinion on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn including whether provisional measures are necessary.

4. Scientific discussion

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

An increased risk for serious cardiac disorders, including myocardial infarction, was identified during the PSUR assessment. This conclusion was 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 (PY), 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 (4 additional events per 1000 PY) was observed in strontium ranelate treated patients compared with placebo treated patients. Among those, myocardial infarction corresponded to 2 additional events per 1000 PY. Further, there was an imbalance of such events both in a study in osteoporotic men, and in a study in osteoarthritis. In addition, given the thrombotic potential of strontium ranelate there was a possible mechanistic rationale for an increased risk for serious cardiac disorders, including myocardial infarction.

Taking into account the efficacy and safety data available at the time, including the newly identified risk for serious cardiac disorders, the PRAC recommended risk minimisation measures to reduce the

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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. In addition to changes to the product information (PI), the PRAC also recommended that strontium ranelate be subject to restricted medical prescription, to additional monitoring and that the MAH conducts a study to assess the effectiveness of the agreed risk minimisation measures.

Following the introduction of the above risk minimisation measures, further in-depth evaluation of the benefits and risks of products containing strontium ranelate was considered necessary and the current procedure under article 20 of Regulation (EC) No 726/2004 was initiated.

4.1. Clinical aspects

Strontium ranelate, the active substance of Protelos/Osseor, is composed of two atoms of stable strontium and one molecule of ranelic acid. Strontium ranelate dissociates at the gastrointestinal level. Strontium is a cation chemically and physiologically closely related to calcium. Ranelic acid is an organic, highly polar molecule without pharmacological activity. It is suggested that strontium acts through dual mechanisms of inhibition of resorption by osteoclasts and maintenance or stimulation of bone formation by osteoblasts. Following the restriction of the indication as a consequence of the PSUR assessment, strontium ranelate (Protelos/Osseor) is currently indicated for:

- Treatment of severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures.
- Treatment of severe osteoporosis in adult men at increased risk of fracture.

The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks.

The postmenopausal osteoporotic (PMO) population dataset for strontium ranelate comprises data from 7 randomised studies: 2 phase II studies CL2-004 (Meunier, 2002; NP07869) and CL2-005 (Reginster 2002; NP08511) and 5 phase III studies CL3-009 (Meunier, 2004; NP08338/NP22819), CL3-010 (Reginster 2005; NP08340/NP22824), CL3-013 (Hwang 2008; NP22514), CL3-015 (Liu 2009; NP25026), CL3-017 (NP24357). This set consisted of 7572 patients (3803 patients treated with strontium ranelate vs. 3769 patients treated with placebo). Details of studies are provided in table 1.

Table 1 OSA2011 - PMO women - description of population included in studies

Studies	Type of study/study objective	Number of patients by treatment group S12911 2g/Placebo	Mean age+/-SD (years) in the S 12911 group	Exposure (days)
CL2-004	To detemine the minimal active dose of strontium ranelate for the curative treatment of established post-menopausal vertebral osteoporosis	87/91	65.6+/-6.9	671.8(202.1)
CL2-005	To detemine the minimal active dose for prevention of bone loss	56/57	54.2+/-3.2	620.5(255.4)
CL3-009	To assess efficacy in reducing vetebral fractures	826/814	69.6+/-7.2	1137.3(519.8)
CL3-010	To assess efficacy in reducing peripheral fractures	2526/2503	76.7+/-5.0	1177.7(702.5)
CL3-013	To assess efficacy on Lumbar BMD in Tawainese patients	67/65	64.3+/-6.7	351.1(76.9)
CL3-015	To assess efficacy on lumbar BMD in Asian patients (China, Malaysia, Hong Kong)	164/165	67.0+/-6.9	360.2(90.2)
CL3-017	To assess efficacy on lumbar BMD in Korean patients	77/74	64.8+/-6.1	340.2(116.4)

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In order to assess the impact of the restrictions introduced in the product information, namely the restriction to patients with severe osteoporosis and patients without the contraindications (current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism; temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest; established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or uncontrolled hypertension), post-hoc subgroup analyses of the existing clinical trial data were performed.

In addition to the contraindication of patients at high cardiovascular risk, another element of the restrictions recently included in the product information was the severity of the disease. The definition of severity of osteoporosis is not universal and can be debated. The PRAC defined the population of severe osteoporosis patients in accordance with the WHO definition i.e. T score ≤ -2.5 SD with 1 or more fragility fractures, but other definitions were also explored by the MAH.

The results of these analyses are presented below.

4.1.1. Clinical safety

Safety overview and discussion

The safety profile of strontium ranelate is characterised by a number of serious risks. VTE has been an identified risk since its approval. In the postmenopausal osteoporotic population, a significant increased risk of venous thrombotic and embolic events was observed in strontium ranelate treated patients as compared to placebo, corresponding to 4 additional events per 1000 patient years (PY). Two of these additional events correspond to VTE. The risk of thromboembolic events was especially high in patients over 80 years of age, which is stated in the current product information.

Among an estimated post-marketing exposure of approximately 3.4 million patient years, 2074 reports have been received on hypersensitivity reactions associated with strontium ranelate. A total of 71 cases were confirmed as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome possibly related to strontium ranelate, and 21 cases were confirmed as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

Other labelled unfavourable effects of strontium ranelate include disturbances in consciousness (common), musculoskeletal pain and creatine kinase increase (common), nausea (common), seizures (uncommon), hepatitis (frequency unknown) and bone marrow failure (frequency unknown). All of these risks can be serious and cause significant problems in daily life, particularly considering a target population of elderly patients.

In order to support the assessment of the overall benefit-risk balance of strontium ranelate in the current indication and with the current restrictions (patients with severe disease without contraindications), a number of exploratory post-hoc subgroup analyses were performed.

The cardiovascular risk in the PMO population without contraindications (current or previous VTE, including deep vein thrombosis and pulmonary embolism; temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest; established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or uncontrolled hypertension) is represented in table 2.

Baseline characteristics of these patients are similar to those of the whole population. Mean duration of treatment was 1057± 654 days (i.e. 2.9 ± 1.8 years), with no relevant differences detected between the two groups.

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No significant difference is identified between strontium ranelate and the placebo group in the incidence of serious emergent cardiac events, myocardial infarction, ischaemic heart disease and thrombotic and embolic arterial events.

Table 2 Cardiovascular risk in the whole PMO population and in whole PMO population without contraindications

		Whole PMO population (N=7572)		Whole PMO without CI (N=4040)	
		S12911 2g (n=3803)	**Placebo (n=3769)**	**S12911 2g (n=2035)**	**Placebo (n=2005)**
Serious cardiac events	Incidence n(%)	262 (6.9)	215 (5.7)	83 (4.1)	73 (3.6)
	Patient Year	23.2	19.1	14.2	12.5
	Odds ratio [95%CI]	1.22[1.02;1.48]		1.13[0.82;1.57]	
	P-value	0.034		0.443	
SMQ MI narrow	Incidence n(%)	64 (1.7)	40 (1.1)	15 (0.7)	15 (0.7)
	Patient Year	5.7	3.6	2.6	2.6
	Odds ratio [95%CI]	1.60[1.07;2.38]		0.99 [0.48;2.04]	
	P-value	0.020		0.988	
SMQ IHD broad (excl. non cardiac CPK)	Incidence n(%)	325 (8.5)	299 (7.9)	79 (7.9)	94 (4.7)
	Patient Year	28.8	26.6	16.5	16.1
	Odds ratio [95%CI]	1.08 [0.92;1.28]		0.82 [061;1.12]	
	P-value	0.337		0.214	
Embolic and thrombotic arterial events (SMQ narrow)	Incidence n(%)	143 (3.8)	132 (3.5)	52 (2.6)	49 (2.4)
	Patient Year	12.7	11.7	8.9	8.4
	Odds ratio [95%CI]	1.08 [0.85;1.37]		1.06 [0.71;4.57]	
	P-value	0.551		0.791	
Cardiovascular EAE leading to death	Incidence n(%)	80 (2.1)	81 (2.1)	28 (1.4)	29 (1.4)
	Patient Year	7.1	7.2	4.8	5.0
	Odds ratio [95%CI]	0.98 [0.71;1.34]		0.96 [0.57;1.61]	
	P-value	0.887		0.866	
Death/Sudden death	Incidence n(%)	18 (0.5)	30 (0.8)	5 (0.2)	12 (0.6)
	Patient Year	1.6	2.7	0.9	2.1
	Odds ratio [95%CI]	0.59 [0.33;1.06]		0.41[0.14;1.17]	
	P-value	0.076		0.085	
Cardiovascular death and non-fatal MI	Incidence n(%)	132 (3.5)	108 (2.9)	41 (2.0)	40 (2.0)
	Patient Year	11.7	9.6	7.0	6.9
	Odds ratio [95%CI]	1.22 [0.94;1.58]		1.02[0.65;1.58]	
	P-value	0.133		0.939	
CNS Haemorrhage and cerebrovascular condition (SMQ narrow)	Incidence n(%)	201 (5.3)	195 (5.2)	87 (4.3)	66 (3.3)
	Patient Year	17.8	17.3	14.8	11.3
	Odds ratio [95%CI]	1.02 [0.83;1.25]		1.33 [0.96;1.84]	
	P-value	0.830		0.091	
SMQ Embolic and thrombotic venous events	Incidence n(%)	71 (1.9)	47 (1.2)	32 (1.6)	26 (1.3)
	Patient Year	6.3	4.2	5.5	4.5
	Odds ratio [95%CI]	1.51[1.04;2.19]		1.22 [0.73;2.06]	
	P-value	0.029		0.448	

Mantel-Haenzel Estimate
p-value associated to the overall treatment effect

In addition to the whole PMO population with or without contraindications, cardiovascular risk was also assessed in the following subpopulations (table 3):

- severe osteoporosis patients (WHO definition, i.e. T score ≤ -2.5 SD with 1 or more fragility fractures) without contraindications

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- severe osteoporosis patients (FRAX[1] definition) i.e. threshold for 'severe osteoporosis' can be defined as the country- and age-specific fracture probability equivalent to a woman with a T-score of less than or equal to – 2.5 SD and a prior fragility fracture, WHO based definition without contraindications

Overall, it can be seen that the odds ratio is usually lower in the restricted populations (regardless of the definition of 'severe osteoporosis' used). However these are post-hoc subgroup analyses and there is uncertainty regarding statistical power considering the restricted sample size and the event rate.

Table 3 Cardiovascular risk in the whole PMO population and in severe PMO population without contraindications according to different definitions (i.e. severe WHO and severe FRAX)

		Whole PMO population (N=7572)		Severe patients (FRAX) without CI (N=2502)		Severe patients (WHO) without CI (N=1952)	
		S12911 2g (n=3803)	Placebo (n=3769)	S12911 2g (n=1243)	Placebo (n=1259)	S12911 2g (n=975)	Placebo (n=977)
Serious cardiac events	Incidence n(%)	262 (6.9)	215 (5.7)	59 (4.7)	49 (3.9)	42 (4.3)	40 (4.1)
	Patient Year	23.2	19.1	16.5	13.7	11.4	13.8
	Odds ratio [95%CI]	1.22 [1.02;1.48]		1.22 [0.82;1.79]		1.05 [0.67;1.64]	
	P-value	0.034		0.323		0.833	
SMQ MI narrow	Incidence n(%)	64 (1.7)	40 (1.1)	12 (1.0)	11 (0.9)	5 (0.5)	6 (0.6)
	Patient Year	5.7	3.6	3.4	3.1	1.7	2.1
	Odds ratio [95%CI]	1.60 [1.07;2.38]		1.10 [0.48;2.52]		0.86 [0.26;2.86]	
	P-value	0.020		0.815		0.807	
SMQ IHD broad (excl. non cardiac CPK)	Incidence n(%)	325 (8.5)	299 (7.9)	54 (4.3)	60 (4.8)	42 (4.3)	56 (5.7)
	Patient Year	28.8	26.6	15.1	16.8	14.4	19.3
	Odds ratio [95%CI]	1.08 [0.92;1.28]		0.91 [0.62;1.32]		0.74 [0.49;1.12]	
	P-value	0.337		0.612		0.150	
Embolic and thrombotic arterial events (SMQ narrow)	Incidence n(%)	143 (3.8)	132 (3.5)	39 (3.1)	32 (2.5)	19 (1.9)	20 (2.0)
	Patient Year	12.7	11.7	10.9	9.0	6.5	6.9
	Odds ratio [95%CI]	1.08 [0.85;1.37]		1.23 [0.76;1.98]		0.96 [0.51;1.82]	
	P-value	0.551		0.394		0.900	
Cardiovascular EAE leading to death	Incidence n(%)	80 (2.1)	81 (2.1)	23 (1.9)	26 (2.1)	13 (1.3)	12 (1.2)
	Patient Year	7.1	7.2	6.4	7.3	4.5	4.1
	Odds ratio [95%CI]	0.98 [0.71;1.34]		0.87 [0.49;1.54]		1.07 [0.49;2.36]	
	P-value	0.887		0.634		0.864	
Death/Sudden death	Incidence n(%)	18 (0.5)	30 (0.8)	3 (0.2)	11 (0.9)	2 (0.2)	5 (0.5)
	Patient Year	1.6	2.7	0.8	3.1	0.7	1.7
	Odds ratio [95%CI]	0.59 [0.33;1.06]		0.27 [0.07;0.96]		0.39 [0.08;2.03]	
	P-value	0.076		0.030		0.248	
Cardiovascular death and non-fatal MI	Incidence n(%)	132 (3.5)	108 (2.9)	33 (2.7)	34 (2.7)	16(1.6)	18 (1.8)
	Patient Year	11.7	9.6	9.2	9.5	5.5	6.2
	Odds ratio [95%CI]	1.22 [0.94;1.58]		0.96 [0.59;1.57]		0.89 [0.45;1.76]	
	P-value	0.133		0.885		0.735	
CNS Haemorrhage and cerebrovascular condition (SMQ narrow)	Incidence n(%)	201 (5.3)	195 (5.2)	57 (4.6)	47 (3.7)	39 (4.0)	31 (3.2)
	Patient Year	17.8	17.3	15.9	13.2	13.4	10.7
	Odds ratio [95%CI]	1.02[0.83;1.25]		1.22[0.82;1.82]		1.29[0.79;2.08]	
	P-value	0830		0.319		0.305	
SMQ Embolic and thrombotic venous events	Incidence n(%)	71 (1.9)	47 (1.2)	19 (1.5)	16 (1.3)	17 (1.7)	16 (1.6)
	Patient Year	6.3	4.2	5.3	4.5	5.8	5.5
	Odds ratio [95%CI]	1.51 [1.04;2.19]		1.18 [0.60;2.31]		1.05 [0.53;2.10]	
	P-value	0.029		0.628		0.882	

Mantel-Haenzel estimate
p-value associated to the overall treatment effect

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Conclusions on Safety

In order to assess whether the restrictions introduced in the product information, namely the restriction to patients with severe osteoporosis and patients without contraindications (current or previous VTE, including deep vein thrombosis and pulmonary embolism; temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest; established, current or past

[1] Risk prediction model which calculates fracture probability using multiple risk factors.

history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or uncontrolled hypertension), post-hoc subgroup analyses of the existing clinical trial data were performed.

Regardless of the definition of severity of osteoporosis used (WHO or FRAX), the estimates of cardiac and thromboembolic risks change in the restricted population when compared to the PMO population. For instance, the estimate of risk for myocardial infarction changes from OR 1.60; 95% CI [1.07; 2.38] in the PMO population to OR 0.86; 95% [0.26; 2.86] in the restricted patient population (severity defined according to WHO definition). However, there are uncertainties regarding statistical power given the restricted sample size and the event rate, and therefore around the reassurance provided by these subgroup analyses.

Furthermore, there are serious concerns about whether the contraindications and warnings implemented to mitigate cardiac and thromboembolic risks could be achievable in clinical practice, considering that strontium ranelate is intended for long-term treatment of a population of elderly patients whose cardiovascular status may deteriorate over time.

The PRAC also took note of all the other risks associated with strontium ranelate (which include serious skin reactions (including DRESS syndrome, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders). All of these risks can be serious and cause significant problems in daily life, particularly considering a target population of elderly patients on long-term treatment.

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4.1.2. Benefit evaluation

Benefit overview and discussion

The analysis of efficacy data across different populations can be seen in table 4.

Table 4 Efficacy in the PMO population and different subgroups

RISK/BENEFIT ASSESSMENT		POST-MENOPAUSAL OSTEOPOROSIS (PMO) POPULATION (N = 7572 PY=22519.6)									
		PMO (N = 7572 PY = 22519.6)		Without CI * (N = 4040 PY = 11690.1)		Without CI and warnings * (N = 3032 PY = 8898.8)		Severe osteoporosis (OP) * (T-score ≤ -2.5 and at least one previous fracture) (N = 3744 PY = 11312.9)		Severe OP (T-score ≤ -2.5 and at least one previous fracture) and without CI and warnings * (N = 1445 PY = 4373)	
		Strontium ranelate 2g N = 3803 PY = 11269.6	Placebo N = 3769 PY = 11250.1	Strontium ranelate 2g N = 2035 PY = 5860.4	Placebo N = 2005 PY = 5829.7	Strontium ranelate 2g N = 1519 PY = 4456.2	Placebo N = 1513 PY = 4442.7	Strontium ranelate 2g N = 1865 PY = 5632.8	Placebo N = 1879 PY = 5680.2	Strontium ranelate 2g N = 718 PY = 2193.1	Placebo N = 727 PY = 2179.9
BENEFIT ASSESSMENT											
Peripheral fracture	N'	3748	3711	2010	1975	1505	1489	1839	1849	711	717
(at least one new)	n (%)	427 (11.4)	492 (13.3)	218 (10.9)	240 (12.2)	160 (10.6)	180 (12.1)	269 (14.6)	293 (15.9)	102 (14.4)	100 (14.0)
	Per 1000 PY	36.7	42.1	36.1	39.6	34.9	39	45.9	49.3	44.7	43.8
	OR [95% CI]	0.841 [0.733 ; 0.966]		0.879 [0.724 ; 1.069]		0.865 [0.690 ; 1.085]		0.910 [0.760 ; 1.089]		1.033 [0.767 ; 1.392]	
	p-value (3)	**0.014**		0.196		0.209		0.303		0.829	
Hip fracture	N'	3748	3711	2010	1975	1505	1489	1839	1849	711	717
(at least one new)	n (%)	111 (3.0)	114 (3.1)	58 (2.9)	52 (2.6)	48 (3.2)	40 (2.7)	67 (3.6)	60 (3.2)	29 (4.1)	17 (2.4)
	Per 1000 PY	9.5	9.8	9.6	9.6	10.5	8.7	11.4	10.1	12.7	7.4
	OR [95% CI]	0.963 [0.739 ; 1.256]		1.099 [0.752 ; 1.606]		1.193 [0.780 ; 1.827]		1.127 [0.791 ; 1.607]		1.751 [0.953 ; 3.216]	
	p-value (3)	0.781		0.627		0.416		0.507		0.071	
Major peripheral fractures	N'	3748	3711	2010	1975	1505	1489	1839	1849	711	717
(at least one new)	n (%)	330 (8.8)	390 (10.5)	166 (8.3)	186 (9.4)	121 (8.0)	137 (9.2)	211 (11.5)	218 (11.8)	75 (10.6)	71 (9.9)
	Per 1000 PY	28.4	33.5	27.6	30.8	26.4	29.8	36.1	36.9	33	31.3
	OR [95% CI]	0.822 [0.705 ; 0.959]		0.866 [0.695 ; 1.078]		0.863 [0.668 ; 1.114]		0.970 [0.793 ; 1.186]		1.073 [0.762 ; 1.511]	
	p-value (3)	**0.013**		0.198		0.258		0.764		0.687	
Vertebral fracture	N'	2917	2939	1588	1599	1175	1205	1488	1514	587	597
(at least one new)	n (%)	507 (17.4)	661 (22.5)	269 (16.9)	355 (22.2)	205 (17.5)	251 (20.8)	386 (25.9)	462 (30.5)	158 (26.9)	167 (28.0)
	Per 1000 PY	48.5	63.7	49.3	64.8	50.5	60.7	70.8	85.8	74.8	80
	OR [95% CI]	0.725 [0.637 ; 0.825]		0.715 [0.599 ; 0.853]		0.803 [0.654 ; 0.986]		0.798 [0.680 ; 0.935]		0.948 [0.735 ; 1.224]	
	p-value (3)	**< 0.001**		**< 0.001**		**0.036**		**0.005**		0.684	

*PMO: post-menopausal women; OP: osteoporosis; EAE: emergent adverse events; MI: myocardial infarction; IHD: ischemic heart disease; * Severe osteoporosis defined as: T-score ≤ -2.5 (Hologic) and at least one previous fracture vertebral or peripheral, CI: contraindications, defined as no medical history of VTE, ischemic heart disease, peripheral arterial disease, cerebrovascular disease, Diastolic Blood Pressure (DBP) < 90 mmHg and Systolic Blood pressure (SBP) < 160 mmHg; No warnings: no medical history of diabetes and dyslipidaemia and no smoking; Number of patients (N) and Number of Patients-Years (PY) by group; n: Number of patients with at least one emergent AE in a given preferred term; %: (n/N)*100; PY: Number of patients per 1000 Patients-Years; N': number of assessable patients for vertebral or peripheral fractures; OR: Odds Ratio; 95%CI: Confidence Interval of the Odds Ratio ; (1) Mantel-Haenszel Estimate;(2) p-value associated to the overall treatment effect; (3): p-value of Chi Square test*

The incidence of all fractures was, as expected, higher in the subgroups with severe osteoporosis

compared to the PMO population. For example, the incidence of vertebral fractures in the strontium ranelate group increased from 48.5 cases per 1000 PY in the whole PMO population to 74.8 cases per 1000 PY in the group with severe osteoporosis and without contraindications and warnings.

In the PMO population, it is estimated that for patients on strontium ranelate there is a reduction of 15 new vertebral fractures, 5 non-vertebral fractures and approximately 0.4[2] hip fractures per 1000 PY (non-significant). No significant differences were seen in the restricted population, however for both peripheral and hip fractures it is noted that the number of events is higher in the strontium ranelate arm in comparison to placebo.

The effect of strontium ranelate in hip fracture in the overall PMO population was noted. The original indication for hip fracture was based on a post-hoc analysis in women > 74 years of age at high fracture risk defined by a femoral neck BMD T-score ≤ -3SD in the TROPOS study. Results showed borderline statistical significance in favour of strontium ranelate. However when all the currently available data are pooled together, and within the severe osteoporosis subpopulation as referred to above, the effect is no longer seen.

Conclusions on Benefits

Radiological vertebral fractures are a common finding in postmenopausal women and are usually asymptomatic. A typical symptomatic vertebral fracture causes acute pain and decreased mobility that lasts about one month. Fractures that require surgery are the most dangerous aspect of osteoporosis. Hip fracture and the following surgery, in particular, are associated with risks such as permanent disability and increased mortality.

Based on the overall fracture data from randomised, placebo-controlled studies in postmenopausal women, strontium ranelate is found to have only a modest benefit in the reduction of fractures, particularly the most serious types of fractures. In the PMO population, the reduction of non-vertebral fractures in strontium ranelate patients compared to placebo was 5 events per 1000 PY, and new vertebral fractures 15 events per 1000 PY. The reduction in hip fractures was approximately 0.4 events per 1000 PY (non-significant).

The recent introduction of restrictions to the therapeutic indication has limited treatment to patients with severe disease and with low baseline cardiac risk, in an attempt to minimise the identified cardiovascular risk. Therefore it was relevant to explore the available data from clinical trials to assess whether the modest benefit identified in the PMO population is maintained in the currently approved population of patients. To this end, exploratory post-hoc subgroup analyses were conducted as new clinical studies are not available. These have limitations due to their unplanned nature and low numbers, however the results raise questions on whether the effect size observed in the whole PMO population is even maintained in the restricted population.

Consultation with external experts

An Ad-Hoc expert group composed of experts from different areas including osteoporosis, cardiology, epidemiology and general practice was convened to provide advice to PRAC. In view of the data provided and other treatment alternatives available, some experts, in particular the experts in osteoporosis, were of the opinion that a patient population could benefit from the product. However the experts considered that, if available, strontium ranelate should only be prescribed as second line treatment in patients with severe osteoporosis as defined by the WHO, and who do not tolerate other alternative treatments. Experts also specified that strontium ranelate should be used only in severe

[2] Analyses in the PMO population were presented with different exposures reflecting different follow-up periods and the reduction in hip fractures varied between 0.3 and 0.4 per 1000 PY (non-significant).

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osteoporosis with significant fragility fracture such as hip and not “trivial” ones such as metacarpal (which was given as an example).

5. Overall discussion and benefit/risk assessment

Strontium ranelate is associated with a number of risks; namely serious cardiac disorders including myocardial infarction, thromboembolic events (including VTE), serious skin reactions (including DRESS syndrome, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders. For the cardiac and thromboembolic events, frequencies have been calculated based on data from controlled clinical studies. In these studies, a statistically significant increase of serious cardiac disorders of 4 events per 1000 PY was observed for the strontium ranelate treated group compared with placebo. Among those, myocardial infarction corresponded to 2 additional events per 1000 PY. The number of additional thromboembolic events associated with strontium ranelate treatment was also 4 per 1000 PY. Among these, VTE corresponded to 2 additional events per 1000 PY.

The MAH provided a set of retrospective subgroup analyses of the PMO studies to consider the impact of excluding patients with contraindications relating to cardiovascular and thromboembolic risks according to the current product information. The exclusion of such patients impacted on the statistical significance of the observed increased risks. However, there is uncertainty regarding the statistical power of the subgroup analyses considering the restricted sample size and the event rate, and therefore around the reassurance provided by these subgroup analyses.

There are serious concerns about whether the contraindications and warnings implemented to mitigate cardiac and thromboembolic risks could be achievable in clinical practice, considering that strontium ranelate is intended for long-term treatment of a population of elderly patients whose cardiovascular status may deteriorate over time.

When fracture data from randomized, placebo-controlled studies in postmenopausal women were reviewed, the magnitude of the benefit of fracture prevention was found to be modest, particularly regarding the most serious types of fractures. The reduction of non-vertebral fractures in strontium ranelate treated patients compared to placebo was 5 events per 1000 PY and new vertebral fracture 15 events per 1000 PY. The reduction in non-vertebral fractures consisted mainly of fractures in ribs-sternum, pelvic-sacrum and humerus. The observed reduction for hip fractures was approximately 0.4 per 1000 PY (non-significant). The new subgroup analyses presented raise questions on whether the effect size observed in the whole PMO population is maintained in the restricted population.

When the identified serious risks, for which there are considerable doubts that they can be adequately mitigated during long-term treatment, are considered in the context of the modest benefit shown in terms of fracture prevention, the benefit/risk balance of strontium ranelate is considered to be not favourable.

The PRAC, having considered the matter, recommended the suspension of the marketing authorisation for Protelos and Osseor. The PRAC considered that, for the suspension to be lifted, additional robust data that enables the identification of a patient population in whom benefits outweigh the risks is needed.

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6. Action plan

6.1. Direct Healthcare Professional Communication

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the suspension of the marketing authorisation for Protelos and Osseor.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities.

7. Conclusion and grounds for the recommendation

Whereas

- The Committee considered Protelos and Osseor (strontium ranelate) in the procedure under Article 20 of Regulation (EC) No 726/2004, initiated by the European Commission.
- The Committee reviewed all data presented by the MAH on the safety and efficacy of strontium ranelate, including retrospective subgroup analyses on the postmenopausal women clinical trial dataset to consider the impact of the restrictions recently introduced on the safety of patients and on the effect size observed.
- The Committee took note of a number of serious risks associated with strontium ranelate, namely serious cardiac disorders (including myocardial infarction), thromboembolic events (including venous thromboembolic events), serious skin reactions (including DRESS syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis), disturbances in consciousness, seizures, hepatitis and blood cytopenic disorders.
- The Committee considered that the exclusion of patients with contraindications relating to cardiovascular and thromboembolic risks impacted on the statistical significance of the observed increased risks. However, there is uncertainty regarding the statistical power of the subgroup analyses considering the restricted sample size and the event rate, and therefore around the reassurance provided by these analyses.
- The Committee also considered that there are serious concerns on whether the contraindications and warnings implemented to mitigate cardiac and thromboembolic risks could be achievable in clinical practice, considering that Protelos and Osseor are intended for long-term treatment of a population of elderly patients whose cardiovascular status may deteriorate over time.
- The Committee considered that, when the fracture data from randomised, placebo-controlled studies in postmenopausal women are reviewed, the magnitude of the benefit in fracture prevention was found to be modest, particularly for the most serious types of fractures. The retrospective subgroup analyses raise questions on whether the effect seen in the postmenopausal population is maintained in the restricted population.
- The Committee concluded that given the number of identified serious risks, for which there are considerable doubts that they can be adequately mitigated during long-term treatment, taking into account the modest benefit shown in terms of fracture prevention, the benefit-risk balance of Protelos and Osseor is not favourable.

The PRAC has therefore recommended the suspension of the marketing authorisation for Protelos and Osseor.

The conditions for lifting the suspension are set out in the Annex II of the recommendation.

The divergent positions are appended to the PRAC recommendation.

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Divergent positions to the PRAC recommendation

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Divergent opinion in favour for a positive benefit/risk balance for strontium ranelate

Divergent statement

Based on the presented evidence in their totality, we are of the following opinion:

- Based on the further data and analyses provided by the MAH, the current risk minimisation measures (introduced following the PSUR procedure finalised in April 2013) appear to reduce the cardiovascular and thromboembolic risk associated with strontium ranelate. The current SmPC restrictions are considered to be feasible in daily clinical practice and their effectiveness can be further explored through the drug utilisation and post-authorisation studies that the MAH has committed to conduct. Use of strontium ranelate under specialist supervision and reservation to last line therapy (where other treatments are contraindicated or not tolerated) could further help to optimise safe and appropriate use.

- Strontium ranelate has demonstrated efficacy in the prevention of fractures, which is considered of comparable magnitude to that of other drugs used in the treatment of osteoporosis. The further analyses submitted by the MAH to determine the impact of the restrictions are of a post-hoc nature but overall they indicate that efficacy is retained in the restricted population.

- Independent experts have highlighted that a patient population could benefit from the product given the contraindications and intolerability of other drugs used for the treatment of osteoporosis. Furthermore, strontium ranelate has a distinct mechanism of action (increasing bone formation as well as decreasing resorption) and in the restricted population it remains an appropriate alternative treatment. Overall the balance of benefits and risks is considered to remain favourable subject to specialist supervision, use as a last line therapy and the current restrictions to reduce cardiovascular and thromboembolic risk.

PRAC members expressing a divergent opinion:

Amy Tanti	07 January 2014	Signature: .....
Gabriela Jazbec	07 January 2014	Signature: .....
Sabine Straus	07 January 2014	Signature: .....
Albert van der Zeijden	07 January 2014	Signature: .....
Julie Williams	07 January 2014	Signature: .....
Filip Babylon	07 January 2014	Signature: .....
Martin Huber	07 January 2014	Signature: .....

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Kamila Czajkowska	07 January 2014	Signature: .....
Harald Herkner	07 January 2014	Signature: .....
George Aislaitner	07 January 2014	Signature: .....
Doris Stenver	07 January 2014	Signature: .....
Eva Jirsovà	07 January 2014	Signature: .....
Margarida Guimarães	07 January 2014	Signature: .....
Andis Lacis	07 January 2014	Signature: .....
Marie L De Bruin	07 January 2014	Signature: .....

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