Annex IV

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

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 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 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.

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.

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 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 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 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.

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.