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Assessment report for Protelos and Osseor

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

INN: Strontium ranelate

Procedure number: Protelos EMEA/H/C/000560/A-20/0034

Procedure number: Osseor EMEA/H/C/000561/A-20/0030

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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1. Background information on the procedure

Protelos/Osseor (strontium ranelate) have been authorised since 2004 for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fracture. Strontium ranelate is made up of two atoms of stable strontium and one molecule of ranelic acid. It is suggested that strontium acts through dual mechanisms of inhibition of resorption by osteoclasts and maintenance or stimulation of bone formation by osteoblasts. Strontium is a cation chemically and physiologically closely related to calcium. Ranelic acid is an organic, highly polar molecule without pharmacological activity.

The risks of venous thromboembolism (VTE) associated with strontium ranelate has been established since the granting of the initial marketing authorisation. Strontium ranelate was associated with an approximately 50% increase in the annual risk for VTE, including pulmonary embolism (PE). This was established during the first year of therapy and appeared to remain unchanged thereafter. Warnings, including risk factors for VTE, were included in the product information. Serious skin reactions, including drug rash with eosinophilia and systemic symptoms (DRESS) were reported rarely in the post-marketing phase. DRESS and other hypersensitivity reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were included in the product information. Both risks, VTE and hypersensitivity reactions, such as DRESS, have been kept under close review by the CHMP, these risks being addressed in the risk management plan for strontium ranelate.

A study recently published in France¹ identified 199 severe adverse reactions following administration of strontium ranelate, of which 52% were cardiovascular events (mostly VTE events) and 26% were cutaneous events. The authors concluded that DRESS syndrome is unpredictable but that the risk of VTE could be reduced by adding a contraindication for patients with a history of VTE and by stopping treatment if a new VTE risk situation occurs.

In view of the above concerns, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 14 October 2011 to assess the above concerns and its impact on the benefit/risk balance of strontium ranelate, and to give its opinion on measures necessary to ensure the safe and effective use of strontium ranelate, and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.

¹ Ranélate de strontium (Protelos): effets indésirables rapporté en France; Presse Med. 2011; 40(10):e453-e462.

2. Scientific discussion

The marketing authorisation holder (MAH) provided relevant information on the risk of VTE and hypersensitivity reactions, such as DRESS, derived from clinical trials, epidemiological studies and spontaneous reports. These were considered in the framework of this review. A summary of the relevant data for this review is presented herein after.

2.1. Clinical aspects

2.1.1. Clinical efficacy

The clinical efficacy of strontium ranelate has been demonstrated and documented through randomised clinical trials in post-menopausal women, by significant reductions in the relative risk of vertebral fractures and non-vertebral fractures, in particular the hip.

2.1.2. Clinical safety

2.1.2.1 Venous thromboembolism (VTE)

Clinical trials and epidemiological studies

The pivotal trials (SOTI and TROPOS) were five-year trials. Both were European multicentre double-blind studies². Strontium ranelate 2 g/d was tested against placebo in elderly Caucasian women on individually titrated calcium and vitamin D supplementation.

The overall safety set of the phase III studies comprised a total of 6669 patients with 3352 strontium ranelate-treated patients and 3317 placebo-treated patients. The age ranged from 50.0 to 100.0 with a mean $\pm$ SD of 75.0 ± 6.4 years in each group. Most of patients (64.4%) were between 70 and 80 (exclusive) years. The Body Mass Index (BMI) ranged from 14.4 to 50.6 kg/m². Approximately 14% of the patients, equally distributed in the 2 groups, were obese (BMI > 30 kg/m²).

In the overall safety assessment over 5 years (6669 osteoporotic postmenopausal patients), the incidence of VTE was 8.5 and 5.9 VTE events/1000 patient-years with strontium ranelate and placebo respectively (relative risk (RR)=1.4, 95% CI = [1.0; 2.0]).

In the most recently completed studies³ (7572 patients) the incidence of VTE was similar at 7.9 and 5.8 VTE events/1000 patient-years with strontium ranelate and placebo (RR=1.37, 95% CI= [0.99; 1.89]; p=0.057). The proportion of PE was 33.7 % in the strontium ranelate group and 29.2 % in the placebo group. The outcome was fatal in 4.8 % of patients in the strontium ranelate group and 8.6% in the placebo group.

Medical history of VTE was shown to be the main risk factor of VTE with a hazard ratio (HR) of 5.0 [3.1; 7.9]. The percentage of patients with a medical history of VTE was 3.13% (in both groups), but in patients who experienced a VTE, this percentage was 14% and the relative risk in patients with history of VTE was 2.51 [0.92; 6.84] compared to 1.22 [0.87; 1.70] in patients without history of VTE.

In the elderly population (age > 80 years), the relative risk of VTE was 1.87 (95% CI = [1.06; 3.31]) in the strontium ranelate treated patients as compared to placebo (the annual incidence of VTE was 17.0/1000 and 9.2/1000 patient-years in the strontium ranelate group and in the placebo group, respectively).

² For details on the initial pivotal trials please refer to the European Public Assessment Report available at www.ema.europa.eu.

³ The most recently completed studies review pooled data from two phase II studies (STRATOS and PREVOS 005) and five phase III studies (including three Asian studies over one year duration in addition to SOTI and TROPOS) in women with osteoporosis. It comprises a total of 7572 patients with 3803 strontium ranelate-treated patients with a mean age $\pm$ SD of 73.7 ± 7.4 and 3769 placebo-treated patients with a mean age $\pm$ SD of 73.8 ± 7.4 . In this safety set, emergent VTE affected 89 (2.3%) patients in the strontium ranelate and 65 (1.7%) patients in the placebo group.

The influence of concomitant medication on the occurrence of VTE was also analysed and overall there was no increased risk of VTE when strontium ranelate was taken with concomitant medication.

Pharmacoepidemiological studies were performed to evaluate the risk of VTE and other medical events in women treated with strontium ranelate in current medical practice.

In the prospective cohort study⁴ (CLE-12911-021), including 12076 patients, VTE was reported in 55 patients (0.46%), giving an incidence of VTE in patients treated with strontium ranelate of 2.1/1000 patient-years. In the whole cohort population, the percentage of patients with a medical history of VTE was 2.3%. Of the 55 patients with VTE, 56% had one or more potential venous thromboembolic risk, such as previous VTE and/or thrombosis (9 patients, 17.0%): deep vein thrombosis (four patients), pulmonary embolism (one patient) and venous thrombosis or phlebitis (four patients); immobilisation (15 patients, 27.0%): due to surgery (uterine surgery, liver surgery, renal surgery and two knee replacement (five patients); fractures (three patients including one who refused anticoagulant prophylaxis and one foot distortion); long bus or train journeys (four patients) and an overall reduction in mobility (three patients hospitalised). Other risk factors of VTE reported in 13 patients were hormone replacement therapy (one patient); obesity (8 patients including one with a history of VTE and two with a history of immobilisation (long bus journey/immobilised by a fracture); and cancers (four patients): breast cancer with liver metastases (one patient hospitalised due to a deterioration in general condition), breast cancer treated with chemotherapy (one patient), endometrial and pancreatic cancer with liver metastases and antiphospholipid antibodies (one patient), cancer of unknown origin with metastasis in liver peritoneum, lymphatic noduli in pleura (one patient).

In the retrospective Prescription-Event Monitoring study (conducted by the Drug Safety Research Unit (DSRU) in the UK) including 10782 patients, the incidence of VTE on strontium ranelate was 6.2/1000 patient-years. Patients were identified from a national prescription file and physicians who prescribed strontium ranelate received one questionnaire for each patient one year after the date of prescription. In this study, there was a history of VTE in 11.6 % of the patients with a VTE.

In the latest analysis (January 2011) from the General Practice Research Database (GPRD) in the UK, the incidence of VTE in strontium ranelate group (N=6454) was similar to the reference cohort of untreated osteoporotic women (n=15846): respectively 8.7 and 8.3 for 1000 patients-year. The main objective of this study was to evaluate and quantify the risk of VTE in women newly treated with strontium ranelate in current medical practice. There was no significant difference in the risk of VTE associated with strontium ranelate when compared to untreated patients (HR=0.82).

The incidence of patients with a medical history of VTE was 3.9 %. The analyses were adjusted for age and the main known other VTE risk factors. The following risk factors and potential confounders were considered: age, history of VTE, hospitalisation (associated risk window of 12 months), fracture (associated risk window of 6 months), major surgery (associated risk window of 6 months), malignant (or unspecified) cancer, inflammatory bowel disease (IBD), varicose veins, heart failure, cerebrovascular disease, atrial fibrillation, number of general practitioner (GP) visits and referrals to specialists (in the 12 months before index date), smoking status, drinking status and consumption level, Body Mass Index (BMI), exposure to Hormone Replacement Therapy (HRT), oral corticosteroids or other antiosteoporotic treatments.

The factors, per se (univariate analysis), that showed the strongest association with the risk of VTE were a history of VTE (HR= 4.36 [3.72; 5.11]), immobilising major surgery (HR= 4.31 [3.36; 5.53]), fracture (4.24 [3.40; 5.29]) or hospitalisation (3.96 [3.48; 4.50]). Increasing age was also associated with an increase risk of VTE.

Post-marketing

A total of 368 spontaneous reports concerning venous thromboembolism events were reported since launch up to September 2011, representing an estimated incidence of 0.14 for 1000 patients-year. A medical history of VTE was found in approximately 13% of patients experiencing VTE. The incidence of PE represented 146 cases among the 368 cases of VTE reported (40 %). A fatal outcome was observed in approximately 9 % of PE cases.

⁴ The post-authorisation study CLE-12911-021 was an observational cohort survey performed in seven European countries in order to evaluate the baseline profile of postmenopausal women treated for osteoporosis in current medical practice and the compliance and tolerability of patients treated with strontium ranelate during long-term follow-up. The safety set defined as at least one follow-up visit and/or medical event notification comprised 12,076 patients. Adverse events were collected at each visit and reported in the electronic case report form designed for the study.

A detailed analysis of spontaneous reports was undertaken. A risk factor for VTE was observed for 31% of the patients with a VTE, with the main risks identified as immobilisation (almost 16% of patients), medical history of VTE (13% of patients) and malignancy (approximately 7% of patients). Risk factors were reported in 34.2% of patients with a PE and 30.1% of patients with deep vein thrombosis. Predisposing factors were reported in 19% of patients with VTE, with obesity and corticosteroid therapy reported in 7.1% and 9.8% of patients, respectively.

The mean time of onset was 273 days after the introduction of treatment with strontium ranelate. The median was 133 days. In most cases (approximately 74%), the event recovered or improved.

Pharmacological studies

Haemostasis has been analysed in pharmacological studies and no clear mechanism which could link strontium ranelate to thromboembolism has been evidenced. In clinical trials, among all haemostasis parameters analysed, there was only an increase in Factor VIII level and a concomitant decrease in Activated partial thromboplastin time (PTT). It is however difficult to evaluate the level of clinical relevance of these changes in terms of VTE risk, especially in the elderly population for which the threshold value for defining "high" FVIII levels is not known. The statistically significant slight shortening of the PTT and the somewhat higher FVIII level among the strontium ranelate treated patients may nevertheless indicate a slight shift in the haemostatic balance towards a more thrombotic state.

Discussion on VTE

Treatment with strontium ranelate within the pivotal clinical trials demonstrated at the time of approval an approximately 50% increase in the annual risk for VTE, including PE. The 5 year-data demonstrated an annual incidence of 8.5/1000 patient-years in the strontium ranelate group versus 5.9/1000 patient-years in the placebo group, with a non-adjusted relative risk of 1.4 in the strontium ranelate treated patients as compared to placebo.

Data pooled from 2 Phase II studies (STRATOS and PREVOS 005) and 5 Phase III studies (including 3 Asian studies over one year duration in addition to SOTI and TROPOS) in women with osteoporosis, the annual incidence of VTE was 7.9/1000 patient-years in the strontium ranelate group versus 5.8/1000 patient-years in the placebo group, with a relative risk of 1.37 in strontium ranelate treated patients as compared to placebo.

In two of the epidemiological studies, the VTE incidence of strontium ranelate exposed patients decreased and was lower or similar to the expected annual incidence in a general population. For the most recent GPRD data, the incidence rate of VTE of the strontium ranelate treated patients was closer to the annual incidence of VTE demonstrated in the clinical trials.

A medical history of VTE was shown to be the main risk factor for VTE. In epidemiological studies, the finding of a history of VTE in patients developing a VTE was also higher compared to the general percentage of the study cohorts. Patients with VTE or a history of VTE should not be prescribed strontium ranelate and therefore the CHMP considers that existing warnings have not been sufficiently effective and that a stronger message should be conveyed to healthcare providers and patients treated with strontium ranelate. In order to further minimise the risk of VTE in this population the CHMP proposes the inclusion of a contraindication. The observed differences concerning the VTE incidence of strontium ranelate exposed patients between the epidemiological studies could also highlight different compliance with the warnings and precautions in prescribing the product. It is therefore appropriate to study such compliance through risk minimisation activities. A prescription survey will be undertaken by the MAH. A draft protocol was considered in the framework of this review. A revised protocol should be included in the next update of the risk management plan.

In the prospective cohort study, including 12076 patients, immobilisation also appeared to be an important risk factor of VTE. This was also identified in data from the post-marketing surveillance, where one third of the post-marketing reports of VTE showed that patients had a history of VTE or other risk factors for VTE, such as immobilisation (e.g. due to fracture, hospitalisation, surgery). The findings support the need of additional risk minimisation measures. Strontium ranelate should not be given to patients temporarily or permanently immobilised, therefore the CHMP considers that the existing warnings should be upgraded to a contraindication in order to minimise the risk of VTE in these patients.

In patients over 80 years the incidence of VTE was higher in the strontium ranelate group in comparison with the placebo-group (RR=1.87). The CHMP therefore considered that appropriate warnings should be included in the product information, with a recommendation to healthcare professionals to re-evaluate the need for continued treatment with strontium ranelate based on individual benefit/risk assessment in patients over 80 years.

The MAH will continue to describe VTE cases in periodic safety update reports (PSURs). Venous thromboembolic data to be provided in PSURs will be classified according to age group (e.g. every 10 years) in order to obtain more information on VTE cases and the risk linked with age. The CHMP considered that mechanistic studies will not provide additional information and therefore further studies are not required. A direct healthcare professional communication (DHPC) should be sent to prescribers to alert them of the key changes to the contraindications (see section 5. Action plan).

2.1.2.2 Hypersensitivity reactions

Clinical trials and epidemiological studies

Data from phase II/III studies and post-authorisation studies were considered. No cases of DRESS, SJS or TEN have been reported in the clinical trial database to date.

Post-marketing

The occurrence of hypersensitivity syndromes such as DRESS and SJS was reported in the post-marketing setting. Since launch up to September 2011, 1736 reported patient cases of hypersensitivity reactions have been identified in the MAH's database. Eight hundred and eight (808) events were considered as serious. An independent panel (expert committee, or EC) selected 380 patient cases for review. The selection was based on whether the associated DRESS symptoms corresponded well with those described by a dedicated severe cutaneous adverse reactions scoring system or if the reactions corresponded to a pre-defined list of serious hypersensitivity events.

Of the 380 patient cases selected by the panel, the review identified a total of 57 cases of DRESS (defined as 11 established, 19 probable and 27 possible cases) for which a relationship to strontium ranelate was considered at least possible, in addition to 10 cases of SJS or TEN. There were four cases of DRESS for which the relationship to strontium ranelate was excluded, 120 cases of drug-induced eruption, 66 cases of cutaneous eruption, 102 cases for which other reasons with or without specific alternative diagnosis were mentioned and 21 cases for which insufficient documentation was provided.

Considering the reported cases, a total of 64 cases were reported as DRESS. There were 22 further cases which were not initially reported as DRESS but which were subsequently reclassified as DRESS following EC evaluation. Therefore, a total of 86 cases of DRESS are considered. The outcome was fatal for four patients, with a direct relationship to DRESS confirmed for one case.

Regarding reported cases of TEN or SJS, a total of 20 cases were initially reported, for which the diagnosis was retained by the EC for 10 of these cases. Out of these 10 cases, three were fatal.

The global incidence of DRESS was calculated as one per 47,168 patient-years of treatment and remained roughly stable over time. The global incidence for SJS and TEN is one per 268,859 patient-years. In future PSURs, the MAH will calculate incidence of newly treated patient number instead of incidence calculations per patient-years.

Non-clinical studies

The potential mechanisms have been studied in non-clinical models. Hypersensitivity reactions cases related to strontium ranelate could be related to strontium or ranelic acid and its metabolites. However, from a non-clinical point of view, no data so far indicated serious hypersensitivity reactions. It was shown in different species (human, monkey, dog, rabbit and rat) that ranelic acid is not metabolised. Moreover it was shown that strontium ranelate has no potential to induce and inhibit drug-metabolising enzymes in human biomaterials *in vitro*. It was noted that strontium is a natural and commonly occurring element.

Discussion on hypersensitivity reactions

The development of hypersensitivity reactions is difficult to predict and depends on individual susceptibility including potentially the presence of genetic predisposition and viral infections. Data from non-clinical studies do not allow identification of a potential mechanism of action for strontium ranelate and there have been no reports of DRESS, SJS or TEN from clinical trials or epidemiologic studies. Notwithstanding these facts, data from the post-marketing setting identified cases of these serious cutaneous hypersensitivity reactions.

The product information already includes skin reactions and reflects the severe hypersensitivity syndromes including DRESS, SJS and TEN, however, its frequency can now be estimated and thus the adverse reactions sections is recommended to be updated: The CHMP considers that the warnings section, which concerned mainly the DRESS syndrome, requires an update. Changes include information to prescribers on key elements of DRESS, SJS and TEN and advice to patients to stop treatment if they develop a hypersensitivity reaction, and that those who have stopped treatment due to hypersensitivity reactions should not re-start therapy with strontium ranelate. Most importantly, prescribers are to advise patients of the time to onset and signs and symptoms of these skin reactions that can be life-threatening.

The CHMP considered that existing risk minimisation activities relating to hypersensitivity reactions are appropriate and no new activities are necessary at this point in time.

2.2. Risk management plan

The MAH submitted a risk management plan (RMP), which included a risk minimisation plan. A tabular summary of the RMP provided for this review is presented below. The new information is presented as grey shaded text in the table below.

Safety concern	Current pharmacovigilance activities (routine and additional)	Current risk minimisation activities (routine and additional)
Identified risks		
Hypersensitivity reactions	In all patients experiencing a severe hypersensitivity reaction: careful monitoring of these events in ongoing and planned strontium ranelate studies using specific questionnaires, as well as in post-marketing experience. All PSURs focus on this issue and analysis of cases are collected whatever the source submission of all cases to a group of independent experts in order to assess the diagnosis of DRESS and the relationship to strontium ranelate. In all patients experiencing severe hypersensitivity reaction type DRESS, TEN or SJS, practitioners in charge of them receive from MAH a letter in which they are strongly recommended to organize and perform blood samplings and cutaneous tests: <i>In order to explore the underlying mechanism (type of reaction)</i> blood sampling for serology and molecular biology search for viruses involved in DRESS reactions (HHV6, HHV7, EBV, CMV) when possible, tissue biopsy	Information included in section 4.4 and 4.8 of the SmPC.

	(skin, adenopathy, liver) for typing the kind of lymphocyte infiltration and viral particles reactivation occurring <i>In order to identify the causal agent</i> <i>in-vitro</i> lymphocyte transformation tests (coupled with an Elispot assay) on T-lymphocytes cells of the patient, in presence of strontium ranelate or each of the suspected concomitant drugs. epicutaneous patch tests with strontium ranelate or each of the concomitant drugs. <i>In order to search for pharmacogenomic risk factors</i> blood sampling for HLA screening (through possible collaboration with the REGISCAR program) In all populations from our clinical trials database extensive exploratory analyses for search of risk factors for hypersensitivity reactions	
VTE	- careful monitoring of all VTE in ongoing and planned strontium ranelate studies - specific questionnaires for venous thromboembolic events for patients having such events and additional biological measurements of haemostasis parameters for at least patients experiencing such events in on going and planned strontium ranelate studies - VTE from all sources are collected and specifically reviewed in the frame work of PSURs. - In order to measure the effectiveness of this new contraindication, a prescription survey will be carried out.	Information included in section 4.4 and 4.8 of the SmPC. Information included in the section 4.3 of the SmPC: Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism. Temporary or permanent immobilisation due to i.e. post-surgical recovery or prolonged bed rest.
Central nervous system disorders including seizures, disturbances in consciousness and memory loss	- careful monitoring of all CNS events such as Seizures, memory loss and disturbances in consciousness in ongoing and planned strontium ranelate studies - specific questionnaires for patients having such events in ongoing and planned studies - seizures, memory loss and disturbances in consciousness from all sources are collected and specifically reviewed in the frame work of PSURs.	Information included in 4.8 of the SmPC.
Creatine Kinase increase and musculoskeletal disorders	- careful monitoring of all muscular events and of all Creatine Kinase increase in ongoing and planned strontium ranelate studies - all PSURs focus on this issue and analysis of all cases are collected whatever the source.	Information included in 4.8 of the SmPC.
Hepatobiliary disorders: Hepatitis and serum transaminases increased (in association with hypersensitivity)	- Routine Pharmacovigilance activities collecting all reports whatever the source - all PSURs focus on this issue and analysis of all cases are collected whatever the source.	Information included in 4.8 of the SmPC.

Psychiatric disorders: confusion, insomnia	- Routine Pharmacovigilance activities collecting all reports whatever the source - all PSURs focus on this issue and analysis of all cases are collected whatever the source.	Information included in 4.8 of the SmPC.
Blood cytopenic disorders: bone marrow failure	- Routine Pharmacovigilance activities collecting all reports whatever the source - All PSURs focus on this issue and analysis of all cases are collected whatever the source.	Information included in 4.8 of the SmPC.
Potential risks		
Interstitial nephritis (renal and urinary disorders)	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Psychiatric disorders: depression and hallucination	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Photosensitivity	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Pancreatitis	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Bone sarcoma	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
HTA	Routine Pharmacovigilance activities collecting all reports whatever the source	Not Applicable
Potential risk of skeletal accumulation of strontium	Measures taken to provide long term data on bone biopsy (i.e., more than 8 years) were proposed in study CL3-12911-012 [SOTI and TROPOS extension phase]. No biopsy was performed. No more measures are planned at this time.	Information included in the section 5.3 of the SmPC.
Missing information		
Paediatric group (<18 years)	Routine pharmacovigilance	Information included in the section 4.2 of the SmPC.
Pregnancy and breast-feeding	Routine pharmacovigilance	Information included in the section 4.6 of the SmPC.

SmPC: summary of product characteristics
PSUR: periodic safety update reports

In order to assess the effectiveness of the proposed contraindications, an additional pharmacovigilance measure was requested. A prescription survey will be carried as detailed above. A draft protocol was considered in the framework of this review. A revised protocol should be included in the next update of the risk management plan.

In addition, the CHMP considered that a direct healthcare professional communication should be sent to prescribers of strontium ranelate, mainly to increase awareness to the new contraindications (see section 5 Action plan).

2.3. Product information

New contraindications were proposed to further reduce the risk of VTE for patients with current or previous VTE and patients temporarily or permanently immobilised. A warning to recommend caution when prescribing strontium ranelate in patients over 80 years was also included. Other amendments were suggested to the product information to bring the list of adverse events and warnings in line with the proposed contraindications.

The skin reactions warnings were updated. Main changes raise awareness to time to onset and signs and symptoms of DRESS, SJS and TEN. Patients experiencing hypersensitivity reactions should discontinue treatment immediately. Patients who developed such reactions in the past must not be

restarted on strontium ranelate. The frequency of reporting of such reactions was reflected in the undesirable effects section.

The package leaflet (PL) was updated accordingly, in line with the proposed changes to the summary of product characteristics (SmPC).

The conditions to the marketing authorisation as laid down in Annex II were updated to reflect the update of the risk management plan and to reflect correctly the frequency of submission of PSURs. Presently PSURs for strontium ranelate are being submitted yearly, but annex II still referred to a 6 monthly submission.

3. Overall discussion and benefit/risk assessment

Strontium ranelate is authorised for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fracture.

Following publication of a study in France⁵, which identified 199 severe adverse reactions reported with strontium ranelate, of which 52% were cardiovascular events (mostly venous thromboembolism) and 26% were cutaneous events, a review to assess the above concerns and their impact on the benefit/risk balance of strontium ranelate was initiated by the European Commission.

The benefits of strontium ranelate have been demonstrated in clinical trials, which sufficiently demonstrated efficacy on the primary endpoints of clinical significance for vertebral and hip fractures in post-menopausal women.

The risk of venous thromboembolism (VTE) associated with strontium ranelate has been known since approval. In the initial clinical trials, treatment with strontium ranelate was associated with approximately 50% increase in the annual risk for VTE, including pulmonary embolism. Warnings were included in the product information, to advise caution in prescribing strontium ranelate to patients at increased risk of VTE, including those with a history of VTE.

Five years long-term follow up safety-data from two phase III studies including 6669 patients (3352 strontium ranelate-treated patients and 3317 placebo-treated patients) demonstrated an annual incidence of 8.5/1000 patient-years in the strontium ranelate group versus 5.9/1000 patient-years in the placebo group, with a non-adjusted relative risk of 1.4 (95% CI = [1.0; 2.0]) in the strontium ranelate treated patients as compared to placebo. A more recent analysis pooled data from two phase II studies and five Phase III studies in women with osteoporosis. It comprised a total of 7572 patients (3803 strontium ranelate-treated patients and 3769 placebo-treated patients), and the annual incidence of VTE was 7.9/1000 patient-years in the strontium ranelate group versus 5.8/1000 patient-years in the placebo group, with a relative risk of 1.37 (95% CI= [0.99; 1.89]; p=0.057) in strontium ranelate treated patients as compared to placebo. These findings were in agreement with the conclusions on the increased risk of VTE associated with strontium ranelate at time of its initial authorisation.

In epidemiological studies the finding of a history of VTE in patients developing a VTE was higher compared to the general percentage of the study cohorts. Immobilisation also appeared to be an important risk factor of VTE, and this was also identified in data from the post-marketing setting, where one third of the post-marketing reports of VTE showed that patients had a history of VTE or other risk factors for VTE. In the elderly population (age > 80 years), the relative risk of VTE was 1.87 (95% CI = [1.06; 3.31]) in the strontium ranelate treated patients as compared to placebo (the annual incidence of VTE was 17.0/1000 and 9.2/1000 patient-years in the strontium ranelate group and in the placebo group, respectively). These findings support the conclusion that - in addition to the increased risk of VTE associated with strontium ranelate as such - a history of VTE and immobilisation are significant risk factors to the development of VTE when taking strontium ranelate. Special attention should also be given to the elderly population, as age may also increase the risk of developing VTE.

The analysis of spontaneous reports also showed that a risk factor for VTE was observed for 31% of the patients with a VTE. The main risks identified from the data included immobilisation and medical history of VTE.

⁵ Ranélate de strontium (Protelos): effets indésirables rapporté en France; Presse Med. 2011; 40(10):e453-e462.

As a consequence, patients with VTE or history of VTE should not be prescribed strontium ranelate. The same restriction should be applied to patients temporarily or permanently immobilised. The Committee for medicinal products for human use (CHMP) therefore recommended the inclusion of new contraindications in the product information. Other relevant sections of the product information, including the warnings and undesirable effects sections, were also updated. In particular, healthcare professionals should re-evaluate the need for continued treatment with strontium ranelate based on individual benefit/risk assessment in patients over 80 years.

The risk management plan reflects these changes and the effectiveness of the measures will be assessed through a prescription survey.

Regarding cutaneous events, the global incidence of hypersensitivity reactions with strontium ranelate appears to be low, the frequency of reporting ranging from very rare to rare. Hypersensitivity reactions cases related to strontium ranelate could be related to strontium or ranelic acid and its metabolites. However, the non-clinical models do not allow identification of a possible mechanism of action.

A total of 86 cases of drug rash with eosinophilia and systemic symptoms (DRESS), and 10 cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been spontaneously reported. No cases were observed in clinical trials or epidemiological studies. It is important that prescribers and patients are aware of the time to onset and signs and symptoms of these skin reactions. Therefore the warnings were updated to convey this message and advise that treatment should be discontinued immediately if symptoms or signs of these conditions are present. Patients who have developed DRESS, SJS or TEN with the use of strontium ranelate must not be re-started on this treatment at any time. The undesirable effects section was also updated to reflect the reported frequency of the hypersensitivity reactions discussed.

Careful monitoring of identified risks, such as VTE and hypersensitivity reactions will continue, and these are appropriately described in the risk management plan.

The Committee considered that prescribers should be made aware of the results of this review, in particular the new contraindication and therefore a direct healthcare professional communication (DHPC) was agreed to be disseminated.

The summary of product characteristics (SmPC) was updated to reflect the proposed new contraindications, revision of warnings and relevant updates to the undesirable effects section, as applicable. The package leaflet (PL) was updated in line with the proposed changes to the SmPC. Annex II was updated to reflect the update of the risk management plan and to reflect the current frequency of submission of PSURs.

Taking all the above into account, the CHMP considers that the benefit risk balance of strontium ranelate is positive under normal conditions of use, subjected to the proposed changes to the product information and the agreed risk management plan.

4. Overall conclusion

Having reviewed all the available data, in particular on VTE and hypersensitivity reactions, provided by the MAH in writing, the CHMP concluded that new contraindications and revised warnings should be included in the product information. Strontium ranelate should not be used in patients with VTE or history of VTE or those temporarily or permanently immobilised. In patients over 80 years at risk of VTE, the need for continued treatment should be re-evaluated. Serious adverse reactions, such as DRESS, SJS and TEN have been reported with the use of strontium ranelate. It is very important that prescribers and patients are aware of the time to onset of these conditions and their signs and symptoms. Treatment should be discontinued if they occur and patients who experienced such adverse events should not be re-treated with strontium ranelate.

A direct healthcare professional communication will be sent out to prescribers in order to raise awareness of the conclusions of this review, in particular the new contraindications. The effectiveness of the contraindications and the communication will be assessed through a prescription survey.

Therefore the CHMP recommends the variation to the terms of the marketing authorisation for which the summary of product characteristics, Annex II and package leaflet is set out in Annex III of the opinion.

The scientific conclusions and the grounds for the amendment of the SmPC, Annex II and package leaflet are set out in Annex IV of the opinion.

5. Action plan

As part of this procedure, the MAH and the CHMP agreed the wording of a 'Dear Healthcare Professional Communication' designed to inform prescribers of the key conclusions of this review, focusing on the new contraindication for strontium ranelate. The letter will be sent to relevant healthcare professionals with dissemination as of 2 April 2012.

6. Conclusion and grounds for the recommendation

The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for strontium ranelate initiated by the European Commission.

The Committee reviewed all data submitted by the marketing authorisation holder, including from non-clinical studies, clinical trials, epidemiological studies and spontaneous reports, in particular on VTE and hypersensitivity reactions.

The Committee concluded that there are risks associated with the use of strontium ranelate, in particular VTE and hypersensitivity reactions. Strontium ranelate should not be used in patients with VTE or history of VTE or those temporarily or permanently immobilised. In patients over 80 years at risk of VTE, the need for continued treatment should be re-evaluated. Serious adverse reactions, such as DRESS, SJS and TEN have been reported with the use of strontium ranelate. It is very important that prescribers and patients are aware of the time to onset of these conditions and their signs and symptoms. Treatment should be discontinued if they occur and patients who experienced such adverse events should not be re-treated with strontium ranelate. The product information (SmPC and PL) as well as the conditions to the marketing authorisation (Annex II), were proposed to be amended accordingly. A correction on the frequency of submission of PSURs was also included in Annex II.

The Committee considered that a direct healthcare professional communication is to be sent out to prescribers in order to raise awareness of the conclusions of this review, in particular the new contraindications. The MAH will conduct a prescription survey in order to explore the effectiveness of the proposed contraindications.

The Committee considered that the efficacy of strontium ranelate has been appropriately demonstrated in clinical trials.

The Committee therefore concluded that the benefit/risk balance of strontium ranelate is positive under normal conditions of use, subjected to the proposed changes to the product information and the agreed risk management plan.

The Committee therefore recommended the variation of the marketing authorisation for strontium ranelate and the amendment of the product information as set out in annexes I, II and IIIB.

The scientific conclusions and the grounds for the amendment of the SmPC, Annex II and package leaflet are set out in Annex IV of the opinion.