ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PROTELOS 2 g granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 2 g of strontium ranelate.

Excipient: Each sachet also contains 20 mg of aspartame (E951).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension
Yellow granules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures (see section 5.1).

4.2 Posology and method of administration

Posology
The recommended dose is one 2 g sachet once daily by oral administration.

Due to the nature of the treated disease, strontium ranelate is intended for long-term use.

The absorption of strontium ranelate is reduced by food, milk and derivative products and therefore, PROTELOS should be administered in-between meals. Given the slow absorption, PROTELOS should be taken at bedtime, preferably at least two hours after eating (see sections 4.5 and 5.2).

Patients treated with strontium ranelate should receive vitamin D and calcium supplements if dietary intake is inadequate.

Elderly population
The efficacy and safety of strontium ranelate have been established in a broad age range (up to 100 years at inclusion) of postmenopausal women with osteoporosis. No dose adjustment is required in relation to age.

Renal impairment
Strontium ranelate is not recommended for patients with severe renal impairment (creatinine clearance below 30 ml/min) (see sections 4.4 and 5.2).No dose adjustment is required in patients with mild-to-moderate renal impairment (30-70 ml/min creatinine clearance) (see section 5.2).

Hepatic impairment
As strontium ranelate is not metabolised, no dose adjustment is required in patients with hepatic impairment.

Paediatric population
The safety and efficacy of PROTELOS in children aged below 18 years have not been established. No data are available.

Method of administration
For oral use.
The granules in the sachets must be taken as a suspension in a glass containing a minimum of 30 ml (approximately one third of a standard glass) of water.
Although in-use studies have demonstrated that strontium ranelate is stable in suspension for 24 hours after preparation, the suspension should be drunk immediately after being prepared.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
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.

4.4 Special warnings and precautions for use

Use in patients with renal impairment

In the absence of bone safety data in patients with severe renal impairment treated with strontium ranelate, PROTELOS is not recommended in patients with a creatinine clearance below 30 ml/min (see section 5.2). In accordance with good medical practice, periodic assessment of renal function is recommended in patients with chronic renal impairment. Continuation of treatment with PROTELOS in patients developing severe renal impairment should be considered on an individual basis.

Venous thromboembolism

In phase III placebo-controlled studies, strontium ranelate treatment was associated with an increase in the annual incidence of venous thromboembolism (VTE), including pulmonary embolism (see section 4.8). The cause of this finding is unknown. PROTELOS is contra-indicated in patients with a past history of venous thromboembolic events (see section 4.3) and should be used with caution in patients at risk of VTE. When treating patients over 80 years at risk of VTE, the need for continued treatment with PROTELOS should be re-evaluated. PROTELOS should be discontinued as soon as possible in the event of an illness or a condition leading to immobilisation (see section 4.3) and adequate preventive measures taken. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. When a VTE occurs, PROTELOS should be stopped**.**

Skin reactions

Life-threatening cutaneous reactions (Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS)) have been reported with the use of PROTELOS.
Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment and usually around 3-6 weeks for DRESS
If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial

nephropathy, interstitial lung disease) are present, PROTELOS treatment should be discontinued immediately.
The best results in managing SJS, TEN or DRESS come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. The outcome of DRESS is favorable in most cases upon discontinuation of PROTELOS and after initiation of corticosteroid therapy when necessary. Recovery could be slow and recurrences of the syndrome have been reported in some cases after discontinuation of corticosteroid therapy.
If the patient has developed SJS, TEN or DRESS with the use of PROTELOS, PROTELOS must not be re-started in this patient at any time.

Interaction with laboratory test
Strontium interferes with colorimetric methods for the determination of blood and urinary calcium concentrations. Therefore, in medical practice, inductively coupled plasma atomic emission spectrometry or atomic absorption spectrometry methods should be used to ensure an accurate assessment of blood and urinary calcium concentrations.

Excipient

PROTELOS contains a source of phenylalanine, which may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Food, milk and derivative products, and medicinal products containing calcium may reduce the bioavailability of strontium ranelate by approximately 60-70%. Therefore, administration of PROTELOS and such products should be separated by at least two hours (see section 5.2).

As divalent cations can form complexes with oral tetracycline and quinolone antibiotics at the gastro-intestinal level and thereby reduce their absorption, simultaneous administration of strontium ranelate with these medicinal products is not recommended. As a precautionary measure, PROTELOS treatment should be suspended during treatment with oral tetracycline or quinolone antibiotics.

An *in vivo* clinical interaction study showed that the administration of aluminium and magnesium hydroxides either two hours before or together with strontium ranelate caused a slight decrease in the absorption of strontium ranelate (20-25% AUC decrease), while absorption was almost unaffected when the antacid was given two hours after strontium ranelate. It is therefore preferable to take antacids at least two hours after PROTELOS. However, when this dosing regimen is impractical due to the recommended administration of PROTELOS at bedtime, concomitant intake remains acceptable.

No interaction was observed with oral supplementation of vitamin D.

No evidence of clinical interactions or relevant increase of blood strontium levels with medicinal products expected to be commonly prescribed concomitantly with PROTELOS in the target population were found during clinical trials. These included: nonsteroidal anti-inflammatory agents (including acetylsalicylic acid), anilides (such as paracetamol), H_2 blockers and proton pump inhibitors, diuretics, digoxin and cardiac glycosides, organic nitrates and other vasodilators for cardiac diseases, calcium channel blockers, beta blockers, ACE inhibitors, angiotensin II antagonists, selective beta-2 adrenoceptor agonists, oral anticoagulants, platelet aggregation inhibitors, statins, fibrates and benzodiazepine derivatives.

4.6 Fertility, pregnancy and lactation

Pregnancy

PROTELOS is only intended for use in postmenopausal women. There are no data from the use of strontium ranelate in pregnant women.
At high doses, animal studies have shown reversible bone effects in the offspring of rats and rabbits treated during pregnancy (see section 5.3). If PROTELOS is used inadvertently during pregnancy, treatment must be stopped.

Breast-feeding
Physico-chemical data suggest excretion of Strontium ranelate in human milk.. PROTELOS should not be used during breast-feeding.

Fertility

No effects were observed on males and females fertility in animal studies.

4.7 Effects on ability to drive and use machines

Strontium ranelate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

PROTELOS has been studied in clinical trials involving nearly 8,000 participants. Long-term safety has been evaluated in postmenopausal women with osteoporosis treated for up to 60 months with strontium ranelate 2 g/day (n=3,352) or placebo (n=3,317) in phase III studies. Mean age was 75 years at inclusion and 23% of the patients enrolled were 80 to 100 years of age.
There were no differences in the nature of adverse reactions between treatment groups regardless of whether patients were aged below or above 80 at inclusion.

Overall incidence rates for adverse reactions with strontium ranelate did not differ from placebo and adverse reactions were usually mild and transient. The most common adverse reactions consisted of nausea and diarrhoea, which were generally reported at the beginning of treatment with no noticeable difference between groups afterwards. Discontinuation of therapy was mainly due to nausea (1.3% and 2.2% in the placebo and strontium ranelate groups respectively).
In phase III studies, the annual incidence of venous thromboembolism (VTE) observed over 5 years was approximately 0.7%, with a relative risk of 1.4 (95% CI = [1.0 ; 2.0]) in strontium ranelate treated patients as compared to placebo (see section 4.4).

The following adverse reactions have been reported during clinical studies and/or post marketing use with Strontium ranelate.
Adverse reactions, defined as adverse events considered at least possibly attributable to strontium ranelate treatment in phase III studies are listed below using the following convention (frequencies *versus* placebo): very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class (SOC) *FREQUENCY CATEGORY*	Percentage of Patients Experiencing the adverse reaction
	Treatment

Adverse Reaction	Strontium ranelate (n=3352)	Placebo (n=3317)
Psychiatric disorders		
Frequency unknown:[a]		
Confusional state	-	-
Insomnia	-	-
Nervous system disorders		
Common:		
Headache	3.3%	2.7%
Disturbances in consciousness	2.6%	2.1%
Memory loss	2.5%	2.0%
Uncommon:		
Seizures	0.4%	0.1%
Vascular disorders		
Common:		
Venous thromboembolism (VTE)	2.7%	1.9%
Respiratory, thoracic and mediastinal disorders		
Frequency unknown:[a]		
Bronchial hyperreactivity	-	-
Gastrointestinal disorders		
Common:		
Nausea	7.1%	4.6%
Diarrhoea	7.0%	5.0%
Loose stools	1.0%	0.2%
Frequency unknown:[a]		
Vomiting	-	-
Abdominal pain	-	-
Oral mucosal irritation (stomatitis and/or mouth ulceration)	-	-
Gastrooesophageal reflux	-	-
Dyspepsia	-	-
Constipation	-	-
Flatulence	-	-
Hepatobiliary disorders		
Frequency unknown:[a]		
Serum transaminase increased (in association with hypersensitivity skin reactions)	-	-
Hepatitis	-	-
Skin and subcutaneous tissue disorders		
Common:		
Dermatitis	2.3%	2.0%
Eczema	1.8%	1.4%
Rare:		
DRESS (see section 4.4)	-	-
Very rare:		
Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4)		
Frequency unknown:[a]		
Hypersensitivity skin reactions (rash, pruritus, urticaria, angioedema)	-	-
	-	-
Alopecia	-	-
Musculoskeletal and connective tissue disorders		
Frequency unknown:[a]		

Musculoskeletal pain (muscle spasm, myalgia, bone pain, arthralgia and pain in extremity)	-	-
General disorders and administration site conditions *Frequency unknown:*[a] Peripheral oedema Pyrexia (in association with hypersensitivity skin reactions)	 -	 -
Blood and Lymphatic disorders *Frequency unknown:*[a] Bone marrow failure Eosinophilia (in association with hypersensitivity skin reactions) Lymphadenopathy (in association with hypersensitivity skin reactions)	 - - -	 - - -
Investigations *Common:* Blood Creatine phosphokinase (CPK) increased[b]	 1.4%	 0.6%

[a] Post-marketing experience

[b] Musculo-skeletal fraction > 3 times the upper limit of the normal range. In most cases, these values spontaneously reverted to normal without change in treatment.

4.9 Overdose

Good tolerance was shown in a clinical study investigating the repeated administration of 4 g strontium ranelate per day over 25 days in healthy postmenopausal women. Single administration of doses up to 11 g in healthy young male volunteers did not cause any particular symptoms.
Following episodes of overdoses during clinical trials (up to 4 g/day for a maximal duration of 147 days), no clinically relevant events were observed.
Administration of milk or antacids may be helpful to reduce the absorption of the active substance. In the event of substantial overdose, vomiting may be considered to remove unabsorbed active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of bone diseases - Other drugs affecting bone structure and mineralisation, ATC code: M05BX03

Mechanism of action

In vitro, strontium ranelate:
- increases bone formation in bone tissue culture as well as osteoblast precursor replication and collagen synthesis in bone cell culture;
- reduces bone resorption by decreasing osteoclast differentiation and resorbing activity.

This results in a rebalance of bone turnover in favour of bone formation.

The activity of strontium ranelate was studied in various non-clinical models. In particular, in intact rats, strontium ranelate increases trabecular bone mass, trabeculae number and thickness; this results in an improvement of bone strength.

In bone tissue of treated animals and humans, strontium is mainly adsorbed onto the crystal surface and only slightly substitutes for calcium in the apatite crystal of newly formed bone. Strontium ranelate does not modify the bone crystal characteristics. In iliac crest bone biopsies obtained after up to 60 months of treatment with strontium ranelate 2 g/day in phase III trials, no deleterious effects on bone quality or mineralisation were observed.

The combined effects of strontium distribution in bone (see section 5.2) and increased X-ray absorption of strontium as compared to calcium, leads to an amplification of bone mineral density (BMD) measurement by dual-photon X-ray absorptiometry (DXA). Available data indicate that these factors account for approximately 50% of the measured change in BMD over 3 years of treatment with PROTELOS 2 g/day. This should be taken into account when interpreting BMD changes during treatment with PROTELOS. In phase III studies, which demonstrated the anti-fracture efficacy of PROTELOS treatment, measured mean BMD increased from baseline with PROTELOS by approximately 4% per year at the lumbar spine and 2% per year at the femoral neck, reaching 13% to 15% and 5% to 6% respectively after 3 years, depending on the study.

In phase III studies, as compared to placebo, biochemical markers of bone formation (bone-specific alkaline phosphatase and C-terminal propeptide of type I procollagen) increased and those of bone resorption (serum C-telopeptide and urinary N-telopeptide cross links) decreased from the third month of treatment up to 3 years.

Secondary to the pharmacological effects of strontium ranelate, slight decreases in calcium and parathyroid hormone (PTH) serum concentrations, increases in blood phosphorus concentrations and in total alkaline phosphatase activity were observed, with no observed clinical consequences.

Clinical efficacy
Osteoporosis is defined as BMD of the spine or hip 2.5 SD or more below the mean value of a normal young population. A number of risk factors are associated with postmenopausal osteoporosis including low bone mass, low bone mineral density, early menopause, a history of smoking and a family history of osteoporosis. The clinical consequence of osteoporosis is fractures. The risk of fractures is increased with the number of risk factors.

Treatment of postmenopausal osteoporosis:
The anti-fracture studies program of PROTELOS was made up of two placebo-controlled phase III studies: SOTI study and TROPOS study. SOTI involved 1,649 postmenopausal women with established osteoporosis (low lumbar BMD and prevalent vertebral fracture) and a mean age of 70 years. TROPOS involved 5,091 postmenopausal women with osteoporosis (low femoral neck BMD and prevalent fracture in more than half of them) and a mean age of 77 years. Together, SOTI and TROPOS enrolled 1,556 patients over 80 years at inclusion (23.1% of the study population). In addition to their treatment (2 g/day strontium ranelate or placebo), the patients received adapted calcium and vitamin D supplements throughout both studies.

PROTELOS reduced the relative risk of new vertebral fracture by 41% over 3 years in the SOTI study (table 1). The effect was significant from the first year. Similar benefits were demonstrated in women with multiple fractures at baseline. With respect to clinical vertebral fractures (defined as fractures associated with back pain and/or a body height loss of at least 1 cm), the relative risk was reduced by 38%. PROTELOS also decreased the number of patients with a body height loss of at least 1 cm as compared to placebo. Quality of life assessment on the QUALIOST specific scale as well as the General Health perception score of the SF-36 general scale indicated benefit of PROTELOS, compared with placebo. Efficacy of PROTELOS to reduce the risk of new vertebral fracture was confirmed in the TROPOS study, including for osteoporotic patients without fragility fracture at baseline.

Table 1: Incidence of patients with vertebral fracture and relative risk reduction

	Placebo	**PROTELOS**	**Relative Risk Reduction vs. placebo (95%CI), p value**
SOTI	N=723	N=719	
New vertebral fracture	32.8%	20.9%	41% (27-52), p<0.001

over 3 years			
New vertebral fracture over the 1st year	11.8%	6.1%	49% (26-64), p<0.001
New clinical vertebral fracture over 3 years	17.4%	11.3%	38% (17-53), p<0.001
TROPOS	N=1823	N=1817	
New vertebral fracture over 3 years	20.0%	12.5%	39% (27-49), p<0.001

In patients over 80 years of age at inclusion, a pooled analysis of SOTI and TROPOS studies showed that PROTELOS reduced the relative risk of experiencing new vertebral fractures by 32% over 3 years (incidence of 19.1% with strontium ranelate vs. 26.5% with placebo).

In an *a-posteriori* analysis of patients from the pooled SOTI and TROPOS studies with baseline lumbar spine and / or femoral neck BMD in the osteopenic range and without prevalent fracture but with at least one additional risk factor for fracture (N=176), PROTELOS reduced the risk of a first vertebral fracture by 72% over 3 years (incidence of vertebral fracture 3.6% with strontium ranelate vs. 12.0% with placebo).

An *a-posteriori* analysis was performed on a subgroup of patients from the TROPOS study of particular medical interest and at high-risk of fracture [defined by a femoral neck BMD T-score ≤ -3 SD (manufacturer's range corresponding to -2.4 SD using NHANES III) and an age ≥ 74 years (n=1,977, i.e. 40% of the TROPOS study population)]. In this group, over 3 years of treatment, PROTELOS reduced the risk of hip fracture by 36% relative to the placebo group (table 2).

Table 2: Incidence of patients with hip fracture and relative risk reduction in patients with BMD ≤ -2.4 SD (NHANES III) and age ≥ 74 years

	Placebo	**PROTELOS**	**Relative Risk Reduction vs. placebo (95%CI), p value**
TROPOS	N=995	N=982	
Hip fracture over 3 years	6.4%	4.3%	36% (0-59), p=0.046

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with PROTELOS in all subsets of the paediatric population in osteoporosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Strontium ranelate is made up of 2 atoms of stable strontium and 1 molecule of ranelic acid, the organic part permitting the best compromise in terms of molecular weight, pharmacokinetics and acceptability of the medicinal product. The pharmacokinetics of strontium and ranelic acid have been assessed in healthy young men and healthy postmenopausal women, as well as during long-term exposure in postmenopausal osteoporotic women including elderly women.

Due to its high polarity, the absorption, distribution and binding to plasma proteins of ranelic acid are low. There is no accumulation of ranelic acid and no evidence of metabolism in animals and humans. Absorbed ranelic acid is rapidly eliminated unchanged via the kidneys.

Absorption
The absolute bioavailability of strontium is about 25% (range 19-27%) after an oral dose of 2 g strontium ranelate. Maximum plasma concentrations are reached 3-5 hours after a single dose of 2 g. Steady state is reached after 2 weeks of treatment. Intake of strontium ranelate with calcium or food reduces the bioavailability of strontium by approximately 60-70%, compared with administration 3 hours after a meal. Due to the relatively slow absorption of strontium, food and calcium intake should be avoided both before and after administration of PROTELOS. Oral supplementation with vitamin D has no effect on strontium exposure.

Distribution
Strontium has a volume of distribution of about 1 l/kg. The binding of strontium to human plasma proteins is low (25%) and strontium has a high affinity for bone tissue. Measurement of strontium concentration in iliac crest bone biopsies from patients treated for up to 60 months with strontium ranelate 2 g/day indicate that bone strontium concentrations may reach a plateau after about 3 years of treatment. There are no data in patients to demonstrate elimination kinetics of strontium from bone off-therapy.

Biotransformation
As a divalent cation, strontium is not metabolised. Strontium ranelate does not inhibit cytochrome P450 enzymes.

Elimination
The elimination of strontium is time and dose independent. The effective half-life of strontium is about 60 hours. Strontium excretion occurs via the kidneys and the gastrointestinal tract. Its plasma clearance is about 12 ml/min (CV 22%) and its renal clearance about 7 ml/min (CV 28%).

Pharmacokinetics in special clinical situations

Elderly
Population pharmacokinetic data showed no relationship between age and apparent clearance of strontium in the target population.

Patients with renal impairment
In patients with mild-to-moderate renal impairment (30-70 ml/min creatinine clearance), strontium clearance decreases as creatinine clearance decreases (approximately 30% decrease over the creatinine clearance range 30 to 70 ml/min) and thereby induces an increase in strontium plasma levels. In phase III studies, 85% of the patients had a creatinine clearance between 30 and 70 ml/min and 6% below 30 ml/min at inclusion, and the mean creatinine clearance was about 50 ml/min. No dosage adjustment is therefore required in patients with mild-to-moderate renal impairment.
There is no pharmacokinetic data in patients with severe renal impairment (creatinine clearance below 30 ml/min).

Patients with hepatic impairment
There is no pharmacokinetic data in patients with hepatic impairment. Due to the pharmacokinetic properties of strontium, no effect is expected.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Chronic oral administration of strontium ranelate at high doses in rodents induced bone and tooth abnormalities, mainly consisting of spontaneous fractures and delayed mineralisation. These effects were reported at bone strontium levels 2-3 times higher than long-term clinical bone strontium levels and were reversible after cessation of treatment.

Developmental toxicity studies in rats and rabbits resulted in bone and tooth abnormalities (e.g. bent long bones and wavy ribs) in the offspring. In rats, these effects were reversible 8 weeks after cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Maltodextrin
Mannitol (E421)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

- 3 years.
- Once reconstituted in water, the suspension is stable for 24 hours. However, it is recommended to drink the suspension immediately after preparation (see section 4.2)

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Paper/polyethylene/aluminium/polyethylene sachets.

Pack sizes
Boxes containing 7, 14, 28, 56, 84 or 100 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/288/001
EU/1/04/288/002
EU/1/04/288/003
EU/1/04/288/004
EU/1/04/288/005
EU/1/04/288/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21/09/2004
Date of renewal: 21/09/2009

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Les Laboratoires Servier Industrie
905, route de Saran
45520 Gidy
France

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system:
The MAH must ensure that the system of Pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, in the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).
In addition, an updated RMP should be submitted :
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities,
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached,
- At the request of the European Medicines Agency.

PSURs
The MAH will continue to submit 1-yearly PSURs, unless otherwise specified by the Committee for Medicinal Products for Human Use (CHMP).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

PROTELOS 2 g granules for oral suspension
Strontium ranelate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 2 g strontium ranelate.

3. LIST OF EXCIPIENTS

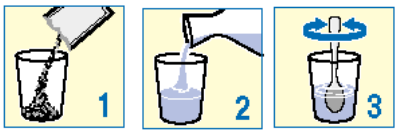
Also contains aspartame (E 951).

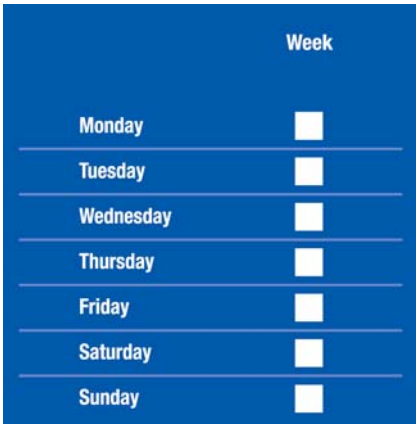
4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension.
7 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use





6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/288/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PROTELOS 2 g

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

PROTELOS 2 g granules for oral suspension
Strontium ranelate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 2 g strontium ranelate.

3. LIST OF EXCIPIENTS

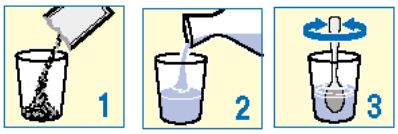
Also contains aspartame (E 951).

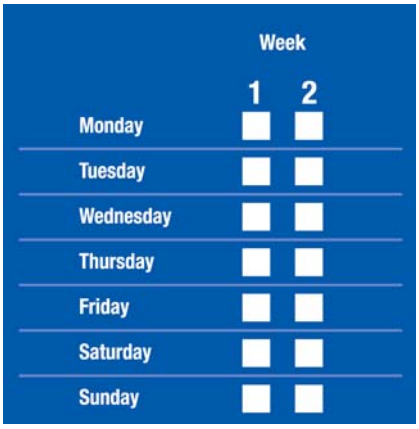
4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension.
14 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use





6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/288/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PROTELOS 2 g

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

PROTELOS 2 g granules for oral suspension
Strontium ranelate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 2 g strontium ranelate.

3. LIST OF EXCIPIENTS

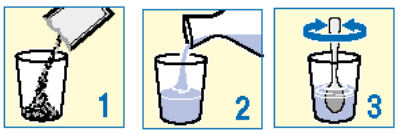
Also contains aspartame (E 951).

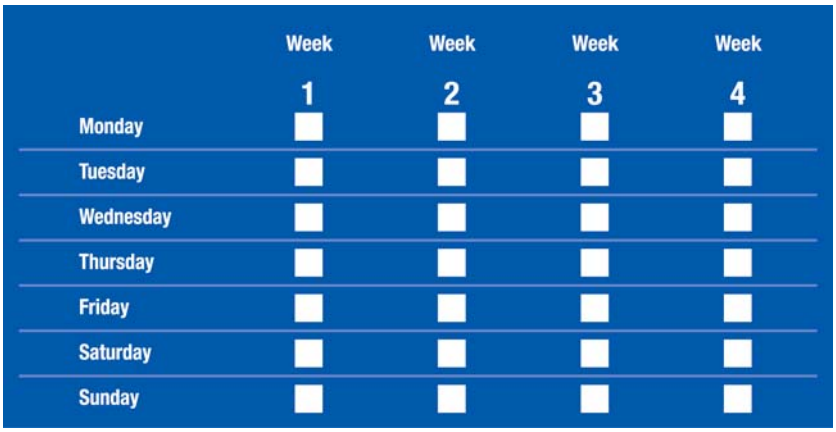
4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension.
28 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use





6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/288/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PROTELOS 2 g

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

PROTELOS 2 g granules for oral suspension
Strontium ranelate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 2 g strontium ranelate.

3. LIST OF EXCIPIENTS

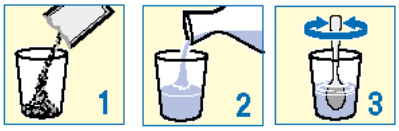
Also contains aspartame (E 951).

4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension.
56 sachets
84 sachets
100 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/288/004 56 sachets
EU/1/04/288/005 84 sachets
EU/1/04/288/006 100 sachets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PROTELOS 2 g

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Sachet

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PROTELOS 2 g granules for oral suspension.
Strontium ranelate.
For oral use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 g

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

PROTELOS 2 g granules for oral suspension

Strontium ranelate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

In this leaflet:

1. WHAT PROTELOS IS AND WHAT IT IS USED FOR

PROTELOS is a non-hormonal medicine used to treat osteoporosis in postmenopausal women.
PROTELOS reduces the risk of fracture at the spine and at the hip.

About osteoporosis
Your body is constantly breaking down old bone and making new bone tissue. If you have osteoporosis, your body breaks down more bone than it forms so that gradually bone loss occurs and your bones become thinner and fragile. This is especially common in women after the menopause
Many people with osteoporosis have no symptoms and you may not even know that you have it. However, osteoporosis makes you more likely to have fractures (break bones), especially in your spine, hips and wrists

How PROTELOS works
PROTELOS, which contains the substance strontium ranelate, belongs to a group of medicines used to treat bone diseases.
PROTELOS works by reducing bone breakdown and stimulating rebuilding of bone and therefore reduces the risk of fracture. The newly formed bone is of normal quality.

2. BEFORE YOU TAKE PROTELOS

Do not take PROTELOS:
- if you are allergic (hypersensitive) to strontium ranelate or any of the other ingredients of PROTELOS.
- if you have or have had a blood clot (for example, in the blood vessels in your legs or lungs).
- if you are immobilised permanently or for some time such as being wheel-chair bound, or confined to bed or if you are to undergo an operation or recovering from an operation. The risk of vein thrombosis (blood clots in the leg or lungs) may be increased in the event of lengthy immobilisation.

Take special care with PROTELOS:
Before taking PROTELOS talk to your doctor :
- if you have severe kidney disease.

During treatment, if you experience an allergic reaction (such as swelling of the face, tongue or throat, difficulty in breathing or swallowing, skin rash), you must immediately stop taking PROTELOS and seek medical advice.
Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis and severe hypersensitivity reactions (DRESS)) have been reported with the use of PROTELOS.
Stevens-Johnson syndrome and toxic epidermal necrolysis appear initially as reddish target-like spots or circular patches often with central blisters on the trunk. Additional signs to look for include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). These potentially life-threatening skin rashes are often accompanied by flu-like symptoms. The rash may progress to widespread blistering or peeling of the skin.
DRESS appears initially as flu-like symptoms and a rash on the face then an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.
The highest risk of occurrence of serious skin reactions is within the first weeks of treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis and usually around 3-6 weeks for DRESS.
If you have developed Stevens-Johnson syndrome or toxic epidermal necrolysis or DRESS with the use of PROTELOS, you must not be re-started on PROTELOS at any time
If you develop a rash or these skin symptoms, stop taking PROTELOS, seek urgent advice from a doctor and tell him that you are taking this medicine.

Use in children
PROTELOS is not intended for use in children and adolescents (below the age of 18).

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

-You should stop taking PROTELOS if you have to take oral tetracyclines or quinolones (two types of antibiotics). You can take PROTELOS again when you have finished taking these antibiotics. If you are unsure about this ask your doctor or pharmacist.

-If you are taking medicines containing calcium, you should leave at least 2 hours before you take PROTELOS.

-If you take antacids (medicines to relieve heartburn) you should take them at least 2 hours after PROTELOS. If this is not possible, it is acceptable to take the two medicines at the same time.

Taking PROTELOS with food and drink:
Food, milk and milk products reduce the absorption of strontium ranelate. It is recommended that you take PROTELOS in-between meals, preferably at bedtime at least two hours after food, milk or milk products or calcium supplements.

Pregnancy and breast-feeding:
PROTELOS is meant for use only in postmenopausal women. Therefore, do not take PROTELOS during pregnancy or when you are breastfeeding. If you take it by accident during pregnancy or breastfeeding, stop taking it straight away and talk to your doctor.

Driving and using machines:
Protelos is unlikely to affect your ability to drive or use machines.

Important information about some of the ingredients of PROTELOS:
PROTELOS contains aspartame. If you suffer from phenylketonuria (a rare, hereditary disorder of the metabolism) talk to your doctor before you start to take this medicine.

3. HOW TO TAKE PROTELOS

Always take PROTELOS exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

PROTELOS is for oral use.
The recommended dose is one 2g sachet a day.

It is recommended that you take PROTELOS at bedtime, preferably at least 2 hours after dinner. You may lie down immediately after taking PROTELOS if you wish.

Take the granules contained in the sachets as a suspension in a glass of water (see instructions below). PROTELOS can interact with milk and milk products, so it is important that you mix PROTELOS only with water to be sure it works properly.

Empty the granules from the sachet into a glass;

Add water;

Stir until the granules are evenly dispersed in the water.

Drink straight away. You should not leave it more than 24 hours before you drink it. If for some reason you cannot drink the medicine straight away, make sure you stir it again before drinking.

Your doctor may advise you to take calcium and vitamin D supplements in addition to PROTELOS. Do not take calcium supplements at bedtime, at the same time as PROTELOS.

Your doctor will tell you how long you should continue to take PROTELOS. Osteoporosis-therapy is usually required for a long period. It is important that you continue taking PROTELOS for as long as your doctor prescribes the medicine.

If you take more PROTELOS than you should:
If you take too many sachets of PROTELOS, tell your doctor or pharmacist. They may advise you to drink milk or take antacids to reduce the absorption of the active ingredient.

If you forget to take PROTELOS:
Do not take a double dose to make up for forgotten individual doses. Just carry on with the next dose at the normal time.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PROTELOS can cause side effects, although not everybody gets them.
The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Common:
Blood clots. Signs of a blood clot include painful swelling in your leg, sudden chest pain or difficulty breathing. See a doctor straight away if you experience any of these symptoms.
Nausea, diarrhoea, headache, skin irritation, memory troubles, fainting fit.
However, these effects were mild and short-lived and usually did not cause the patients to stop taking their treatment. Talk to your doctor if any effects become troublesome or persist.

Uncommon:
Seizures.

Rare:
Severe hypersensitivity reactions (DRESS: see section 2)

Very rare:
Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported (see section 2).

Not known:
Vomiting, abdominal pain, reflux, indigestion, constipation, flatulence, difficulty in sleeping, inflammation of the liver (hepatitis), oral irritation (such as mouth ulcers and gum inflammation), bone, muscle and/or joint pain, muscle cramps, hair loss, reduction in production of blood cells in the bone marrow, itching, hives, blistering, angioedema (such as swollen face, tongue or throat, difficulty in breathing or swallowing), swelling in limbs, feeling confused, bronchial hyperreactivity (symptoms include wheezing and shortness of breath).

If you have stopped treatment due to hypersensitivity reactions, do not take PROTELOS again.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PROTELOS

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use after the expiry date which is stated on the box and the sachet after EXP.
Once reconstituted in water, the suspension is stable for 24 hours. However, it is recommended to drink the suspension immediately after preparation (see section 3)

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What PROTELOS contains
- The active substance is strontium ranelate. Each sachet contains 2 g of strontium ranelate.
- The other ingredients are aspartame (E 951), maltodextrin, mannitol (E 421).

What PROTELOS looks like and contents of the pack
PROTELOS is available in sachets containing yellow granules for oral suspension**.** PROTELOS is supplied in boxes of 7, 14, 28, 56, 84 or 100 sachets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

Manufacturer
Les Laboratoires Servier Industrie
905, route de Saran
45520 Gidy
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
S.A. Servier Benelux N.V.
Tel: +32 (0)2 529 43 11

Luxembourg/Luxemburg
S.A. Servier Benelux N.V.
Tel: +32 (0)2 529 43 11

България
Сервие Медикал ЕООД
Тел.: +359 2 921 57 00

Magyarország
Servier Hungaria Kft.
Tel: +36 1 238 7799

Česká republika
Servier s.r.o.
Tel: +420 222 118 111

Malta
Galepharma Ltd
Tel: +(356) 21 247 082

Danmark
Servier Danmark A/S
Tlf: +45 36 44 22 60

Nederland
Servier Nederland Farma B.V.
Tel: +31 (0)71 5246700

Deutschland
Servier Deutschland GmbH
Tel: +49 (0)89 57095 01

Norge
Servier Danmark A/S
Tlf: +45 36 44 22 60

Eesti
CentralPharma Communications OÜ
Tel: +372 640 00 07

Österreich
Servier Austria GmbH
Tel: +43 (1) 524 39 99

Ελλάδα
ΣΕΡΒΙΕ ΕΛΛΑΣ ΦΑΡΜΑΚΕΥΤΙΚΗ ΕΠΕ
Τηλ: +30 210 939 1000

España
Laboratorios Servier S.L.
Tel: +34 91 748 96 30

France
Les Laboratoires Servier
Tel: +33 (0)1 55 72 60 00

Ireland
Servier Laboratories (Ireland) Ltd.
Tel: +353 (0)1 6638110

Ísland
Servier Laboratories
c/o Icepharma hf
Sími: +354 540 8000

Italia
Servier Italia S.p.A.
Tel: +39 (06) 669081

Κύπρος
Χ.Α.Παπαέλληνας & Σία Λτδ
Τηλ: +357 22741741

Latvija
SIA Servier Latvia
Tel. +371 67502039

Lietuva
UAB "SERVIER PHARMA"
Tel: +370 (5) 2 63 86 28

Polska
Servier Polska Sp. z o.o.
Tel: +48 (0) 22 594 90 00

Portugal
Servier Portugal, Lda
Tel.: +351 21 312 20 00

România
Servier Pharma SRL
Tel: +40 21 528 52 80

Slovenija
Servier Pharma d.o.o.
Tel.: +386 (0)1 563 48 11

Slovenská republika
Servier Slovensko spol. s r.o.
Tel.:+421 (0)2 5920 41 11

Suomi/Finland
Servier Finland Oy
Puh/Tel: +358 (0)9 279 80 80

Sverige
Servier Sverige AB
Tel: +46 (8) 52 25 08 00

United Kingdom
Servier Laboratories Ltd
Tel: +44 (0)1753 666409

This leaflet was last approved in{date}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, ANNEX II AND PACKAGE LEAFLET PRESENTED BY THE EUROPEAN MEDICINES AGENCY

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF PROTELOS (STRONTIUM RANELATE)

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 France[1], 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 clinically 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.

[1] 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 convene 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 update 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.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, ANNEX II AND PACKAGE LEAFLET

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 summary of product characteristics, Annex II and package leaflet are set out in Annex IV of the opinion.