ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 with known effect:
Each sachet also contains 20 mg of aspartame (E951).

For the 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 severe osteoporosis:
- in postmenopausal women,
- in adult men,

at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. In postmenopausal women, strontium ranelate reduces the risk of vertebral and hip fractures (see section 5.1).
The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Treatment should only be initiated by a physician with experience in the treatment of osteoporosis.

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
The efficacy and safety of strontium ranelate have been established in a broad age range (up to 100 years at inclusion) of adult men and 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 sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment (see section 5.2).

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 listed in section 6.1.
- Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.
- Temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest.
- Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Uncontrolled hypertension.

4.4 Special warnings and precautions for use

Cardiac ischaemic events
In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in PROTELOS treated patients compared to placebo (see section 4.8).
Before starting treatment, patients should be evaluated with respect to cardiovascular risk.
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration (see sections 4.3 and 4.8).
During PROTELOS treatment, these cardiovascular risks should be monitored on a regular basis generally every 6 to 12 months.
Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled (see section 4.3).

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**.**

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.

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.
A higher incidence, although still rare, of hypersensitivity reactions including skin rash, SJS or TEN in patients of Asian origin has been reported (see section 4.8).
HLA-A*33:03 and HLA-B*58:01 alleles have been identified as potential genetic risk factors for strontium ranelate-associated SJS/TEN in Han Chinese patients from a retrospective, case-control, pharmacogenetic study. Where possible, screening for HLA-A*33:03 and HLA-B*58:01 alleles could be considered before starting treatment with PROTELOS in patients of Han Chinese origin. If tests are positive for one or both alleles, PROTELOS should not be started. However, absence of these alleles upon genotyping does not exclude that SJS/TEN can still occur.

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 aspartame, 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 sections 4.2 and 5.2).

As divalent cations can form complexes with oral tetracycline (e.g. doxycycline) and quinolone antibiotics (e.g. ciprofloxacin) 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
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

Summary of the safety profile
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.

In a pooled analysis of randomised placebo-controlled studies in post-menopausal osteoporotic patients , 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.
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.

Tabulated list of adverse reactions
The following adverse reactions have been reported during clinical studies and/or post marketing use with strontium ranelate.
Adverse reactionsare listed below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic disorders	Uncommon	Lymphadenopathy (in association with hypersensitivity skin reactions)
	Rare	Bone marrow failure#
		Eosinophilia (in association with hypersensitivity skin reactions)
Metabolism and nutrition disorders	Common	Hypercholesterolaemia
Psychiatric disorders	Common	Insomnia
	Uncommon	Confusion
Nervous system disorders	Common	Headache
		Disturbances in consciousness
		Memory loss
		Dizziness
		Paraesthesia
	Uncommon	Seizures
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Myocardial infarction
Vascular disorders	Common	Venous thromboembolism (VTE)
Respiratory, thoracic and mediastinal disorders	Common	Bronchial hyperreactivity
Gastrointestinal disorders	Common	Nausea
		Diarrhoea and Loose stools
		Vomiting
		Abdominal pain
		Gastrointestinal pain
		Gastrooesophageal reflux
		Dyspepsia
		Constipation
		Flatulence
	Uncommon	Oral mucosal irritation (stomatitis and/or mouth ulceration)
		Dry mouth
Hepatobiliary disorders	Common	Hepatitis
	Uncommon	Serum transaminase increased (in association with hypersensitivity skin reactions)
Skin and subcutaneous tissue disorders	Very common	Hypersensitivity skin reactions (rash, pruritus, urticaria, angioedema)[§]
	Common	Eczema
	Uncommon	Dermatitis
		Alopecia

	Rare	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4)#
	Very rare	Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome and toxic epidermal necrolysis* (see section 4.4)#
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain (muscle spasm, myalgia, bone pain, arthralgia and pain in extremity)[§]
General disorders and administration site conditions	Common	Peripheral oedema
	Uncommon	Pyrexia (in association with hypersensitivity skin reactions)
		Malaise
Investigations	Common	Blood Creatine phosphokinase (CPK) increased[a]

[§] Frequency in Clinical Trials was similar in the drug and placebo group.
* In Asian countries reported as rare
# For adverse reaction not observed in clinical trials, the upper limit of the 95% confidence interval is not higher than 3/X with X representing the total sample size summed up across all relevant clinical trials and studies.
[a] 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.

Description of selected adverse reactions
Venous thromboembolism
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).

Myocardial infarction
In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in strontium ranelate treated patients as compared to placebo (1.7% versus 1.1 %), with a relative risk of 1.6 (95% CI = [1.07 ; 2.38]).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
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.

Management
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

Study	Placebo	PROTELOS	Relative Risk Reduction vs. placebo (95%CI), p value
SOTI	N=723	N=719	
New vertebral fracture over 3 years	32.8%	20.9%	41% (27-52), p<0.001
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

Study	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

Treatment of Osteoporosis in men:
The efficacy of PROTELOS was demonstrated in men with osteoporosis in a 2-year, double-blind,placebo-controlled study with a main analysis after one year in 243 patients (Intention to treatpopulation, 161 patients received strontium ranelate) at high risk of fracture (mean age 72,7 years; mean lumbar BMD T-score value of -2.6; 28% of prevalent vertebral fracture).
All patients received daily supplemental calcium (1000 mg) and vitamin D (800 UI).
Statistically significant increases in BMD were observed as early as 6 months following initiation of PROTELOS treatment versus placebo.
Over 12 months, a statistically significant increase in mean lumbar spine BMD, main efficacy criteria (E (SE) = 5.32% (0.75); 95%CI = [3.86 ; 6.79]; p<0,001), similar to that observed in the pivotal anti-fracture phase III studies carried-out inpostmenopausal women, was observed.
Statistically significant increases in femoral neck BMD and total hip BMD (p<0,001) were observed after 12 months.

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 men with osteoporosis and 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 populations

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

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).

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 that were reversible after cessation of treatment. These effects were reported at bone strontium levels 2-3 times higher than bone strontium levels in humans up to 3 years of treatment. The data on skeletal strontium ranelate accumulation in longer term exposure is limited.

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.

Environmental Risk Assessment (ERA)
The environmental risk assessment of strontium ranelate has been conducted in accordance to European guidelines on ERA.
Strontium ranelate does not present a risk for the environment.

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.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

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 latest renewal: 22/05/2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Les Laboratoires Servier Industrie, 905, route de Saran - 45520 Gidy, France
Przedsiebiorstwo Farmaceutyczne ANPHARM S.A., ul. Annopol 6B – 03-236 Warszawa, Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description
Non-interventional safety study to evaluate the effectiveness of the applied risk minimisation measures, including a description of the treated patient population in everyday clinical practice, patterns of use and cardiovascular risk. After approval of the protocol, annual reports from this study shall be provided within the PSUR until submission of the final study report, which is due by December 2017.

Additional risk minimisation measures

In each Member State where PROTELOS is marketed, the Marketing Authorisation Holder (MAH) shall agree the final educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authority in each Member State where PROTELOS is marketed, all physicians who are expected to prescribe PROTELOS are provided with the following educational package:

- SmPC
- Package leaflet
- Prescriber guide and checklist
- Patient alert card

The prescriber guide and checklist shall contain the following key messages:

- PROTELOS is only indicated for use in patients with severe osteoporosis at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.
- The initiation of treatment with PROTELOS should be based on an assessment of the individual patient's overall risk.
- All patients should be fully informed that cardiovascular risks should be monitored on a regular basis generally every 6-12 months.
- The patient alert card should be given to every patient.
- PROTELOS is contraindicated and must not be used in patients with :
    - Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
    - Uncontrolled hypertension.
    - 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.
    - Hypersensitivity to the active substance (strontium ranelate) or any of the excipients.
- PROTELOS should only be used with caution in:
    - Patients with significant risk factors for cardiovascular events such as hypertension, hyperlipidaemia, diabetes mellitus or smoking.
    - 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.
- The treatment should be either discontinued or stopped in the following situations:
    - If the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled, the treatment should be stopped.
    - As soon as possible in the event of an illness or a condition leading to immobilization, the treatment should be discontinued.
    - If symptoms or signs of Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug Rash with Eosinophilia and Systemic Symptoms (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. If the

patient has developed SJS, TEN or DRESS with the use of PROTELOS, PROTELOS must not be re-started.

- Within the prescriber guide there will be a check-list to remind prescribers of the contraindications, warnings and precautions prior to prescribing and to support the regular monitoring of cardiovascular risk.

The patient alert card shall contain the following key messages:

- Importance of showing the patient alert card to any Health Care Professional involved in their treatment.
- The contraindications to the treatment with PROTELOS.
- Key signs and symptoms of myocardial infarction, VTE and serious skin reactions.
- When to seek urgent medical advice.
- Importance of regularly monitoring cardiovascular risk.

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

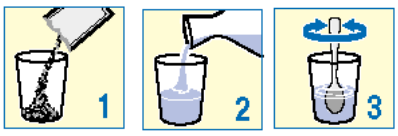
Also contains aspartame (E 951).

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
If not used immediately after reconstitution, the preparation should be consumed within 24 hours.

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

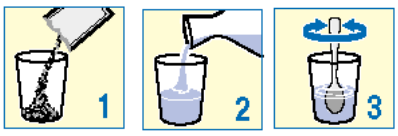
Also contains aspartame (E 951).

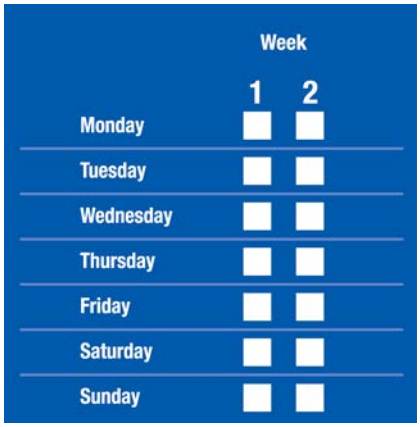
4. PHARMACEUTICAL FORM AND CONTENTS

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
If not used immediately after reconstitution, the preparation should be consumed within 24 hours.

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

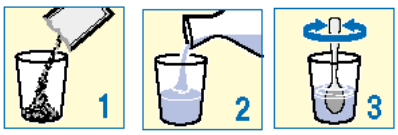
Also contains aspartame (E 951).

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



	Week 1	Week 2	Week 3	Week 4
Monday	☐	☐	☐	☐
Tuesday	☐	☐	☐	☐
Wednesday	☐	☐	☐	☐
Thursday	☐	☐	☐	☐
Friday	☐	☐	☐	☐
Saturday	☐	☐	☐	☐
Sunday	☐	☐	☐	☐

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
If not used immediately after reconstitution, the preparation should be consumed within 24 hours.

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

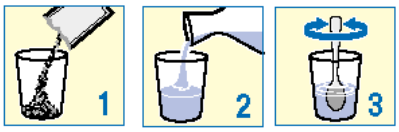
Also contains aspartame (E 951).

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
If not used immediately after reconstitution, the preparation should be consumed within 24 hours.

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 (3 packs of 28)
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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 g

6. OTHER

Read the package leaflet before use

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

PROTELOS 2 g granules for oral suspension
Strontium ranelate

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What PROTELOS is and what it is used for

PROTELOS is a medicine used to treat severe osteoporosis:
- in postmenopausal women,
- in adult men,

at high risk of fracture, for whom other alternative treatments are not possible. In postmenopausal women, strontium ranelate 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. What you need to know before you take PROTELOS

Do not take PROTELOS:

- if you are allergic to strontium ranelate or any of the other ingredients of PROTELOS (listed in section 6).
- 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.
- if you have established ischaemic heart disease, or cerebrovascular disease, e.g. you have been diagnosed with a heart attack, stroke, or transient ischaemic attack (temporary reduction of blood flow to the brain; also known as "mini-stroke"), angina, or blockages of blood vessels to the heart or brain.
- if you have or have had problems with your blood circulation (peripheral arterial disease) or if you have had surgery on the arteries of your legs.
- if you have high blood pressure not controlled by treatment.

Warnings and precautions:
Talk to your doctor or pharmacist before taking PROTELOS:
- if you are at risk of heart disease, this includes high blood pressure, high cholesterol, diabetes, smoking.
- if you are at risk of blood clots.
- if you have severe kidney disease.

Your doctor will evaluate the conditions of your heart and blood vessels regularly, generally every 6 to 12 months for as long you are taking PROTELOS.

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 (see section 4).
Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis and severe hypersensitivity reactions (DRESS)) have been reported with the use of PROTELOS.
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 develop a rash or serious skin symptoms (see section 4), stop taking PROTELOS, seek urgent advice from a doctor and tell him that you are taking this medicine.
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 are of Asian origin, you may be at higher risk of skin reactions.
The risk of these skin reactions in patients of Asian origin, particularly Han Chinese, may be predicted. Patients who have the HLA-A*33:03 and/or the HLA-B*58:01 genes are more likely to develop a serious skin reaction than those who do not have the genes.
Your doctor should be able to advise if a blood test is necessary before taking PROTELOS.

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

Other medicines and PROTELOS:
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
You should stop taking PROTELOS if you have to take oral tetracyclines such as doxycycline or quinolones such as ciprofloxacin (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.

If you need to have blood or urine tests to check your level of calcium, you should tell the laboratory that you are taking PROTELOS as it may interfere with some testing methods.

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:
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.

PROTELOS contains aspartame (E951):
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

The treatment should only be started by a doctor with experience in treating osteoporosis.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

PROTELOS is for oral use.
The recommended dose is one 2 g 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 containing a minimum of 30 ml (approximately one third of a standard 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 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 more sachets of PROTELOS than recommended by your doctor, 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.

If you stop taking PROTELOS:
It is important that you continue taking PROTELOS for as long as your doctor prescribes the medicine. PROTELOS can treat your severe osteoporosis only if you continue to take it.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If the following happens to you, stop using PROTELOS and talk to your doctor immediately:

Common (may affect up to 1 in 10 people):
- Heart attack: sudden crushing pains in your chest which may reach your left arm, jaw, stomach, back and/or shoulders. Other symptoms may be nausea/vomiting, sweating, shortness of breath, palpitations, (extreme) tiredness and/or dizziness. Heart attack may occur commonly in patients at high risk for heart disease. Your doctor will not prescribe PROTELOS for you if you are at particular risk.
- Blood clots in veins: pain, redness, swelling in your leg, sudden chest pain or difficulty breathing.

Rare (may affect up to 1 in 1000 people):
- Signs of severe hypersensitivity reactions (DRESS): initially as flu-like symptoms and a rash on the face then an extended rash with a high temperature (*uncommon*), increased levels of liver enzymes seen in blood tests (*uncommon*) an increase in a type of white blood cell (eosinophilia) (*rare*) and enlarged lymph nodes (*uncommon*).

Very rare (may affect up to 1 in 10,000 people):
- Signs of potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis): initially as reddish target-like spots or circular patches often with central blisters on the trunk. Additional signs may 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.

Other possible side effects

Very Common (may affect more than 1 in 10 people):

Itching, hives, skin rash, angioedema (such as swollen face, tongue or throat, difficulty in breathing or swallowing), bone, limb, muscle and/or joint pain, muscle cramps.

Common:
Vomiting, abdominal pain, reflux, indigestion, constipation, flatulence, difficulty in sleeping, inflammation of the liver (hepatitis), swelling in limbs, bronchial hyperreactivity (symptoms include wheezing and shortness of breath and cough), increased level of a muscle enzyme (Creatine phosphokinase), increased levels of cholesterol.
Nausea, diarrhoea, headache, eczema, memory trouble, fainting fit, pins and needles, dizziness, vertigo. 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 (may affect up to 1 in 100 people):
Seizures, oral irritation (such as mouth ulcers and gum inflammation), hair loss, feeling confused, feeling unwell, dry mouth, skin irritation.

Rare:
Reduction in production of blood cells in the bone marrow.

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

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PROTELOS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the box and the sachet after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other 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(s)
Les Laboratoires Servier Industrie
905, route de Saran
45520 Gidy
France

Anpharm Przedsiebiorstwo Farmaceutyczne S.A.
03-236 Warszawa
ul. Annopol 6B
Poland

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

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

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

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

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

Eesti
Servier Laboratories OÜ
Tel:+ 372 664 5040

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

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

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

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

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

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

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

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

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

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

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

Hrvatska
Servier Pharma, d. o. o.
Tel.: +385 (0)1 3016 222

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
C.A. Papaellinas Ltd.
Τηλ: +357 22741741

Latvija
SIA Servier Latvia
Tel. +371 67502039

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
P./Tel: +358 (0)9 279 80 80

Sverige
Servier Sverige AB
Tel: +46 (0)8 522 508 00

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

This leaflet was last revised in

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