

1. NAME OF THE MEDICINAL PRODUCT

PROTELOS 2g 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 daily 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 dosage 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 dosage adjustment is required in patients with hepatic impairment.

Use in children and adolescents

PROTELOS is not recommended for use in children and adolescents (below the age of 18) due to a lack of data on safety and efficacy.

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.

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 should be used with caution in patients at increased risk of VTE, including patients with a past history of VTE. When treating patients at risk, or developing risk of VTE, particular attention should be given to possible signs and symptoms of VTE and adequate preventive measures taken.

Skin reactions

Cases of severe hypersensitivity syndromes, including, in particular, drug rash with eosinophilia and systemic symptoms (DRESS), sometimes fatal, have been reported with the use of PROTELOS (see section 4.8). The DRESS syndrome is characterised by rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease). Time to onset was usually around 3-6 weeks and the outcome in most cases favourable upon discontinuation of PROTELOS and after initiation of corticosteroid therapy. Recovery could be slow and recurrences of the syndrome have been reported in some cases after discontinuation of corticosteroid therapy.

Patients should be informed to stop PROTELOS immediately and permanently when a rash occurs and to seek medical advice. Patients who have stopped treatment due to hypersensitivity reactions or other serious allergic reactions should not re-start therapy with PROTELOS.

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 gastrointestinal 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), H2 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 Pregnancy and lactation

PROTELOS is only intended for use in postmenopausal women.

No clinical data on exposed pregnancies are available for strontium ranelate. 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.

Strontium is excreted in milk. Strontium ranelate must not be given to nursing women.

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 events with strontium ranelate did not differ from placebo and adverse events 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).

System Organ Class (SOC)	Percentage of Patients Experiencing the ADR	
	Treatment	
Frequency category	Strontium ranelate (n=3352)	Placebo (n=3317)
Adverse Drug Reaction		
Nervous system disorders		
<i>Common:</i>		
Headache	3.3%	2.7%
Disturbances in consciousness	2.6%	2.1%
Memory loss	2.5%	2.0%
<i>Uncommon:</i>		
Seizures	0.4%	0.1%
Gastrointestinal disorders		
<i>Common:</i>		
Nausea	7.1%	4.6%
Diarrhoea	7.0%	5.0%
Loose stools	1.0%	0.2%
<i>Frequency unknown:^a</i>		
Vomiting	—	—
Abdominal pain	—	—
Oral mucosal irritation (stomatitis and/or mouth ulceration)	—	—
Hepatobiliary disorders		
<i>Frequency unknown:^a</i>		
Serum transaminase increased (in association with hypersensitivity skin reactions)	—	—
Skin and subcutaneous tissue disorders		
<i>Common:</i>		
Dermatitis	2.3%	2.0%
Eczema	1.8%	1.4%
<i>Frequency unknown:^a</i>		
Hypersensitivity skin reactions (rash, pruritus, urticaria, angioedema)	—	—
Severe hypersensitivity syndromes including Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS (see Section 4.4)	—	—
Musculoskeletal and connective tissue disorders		
<i>Frequency unknown:^a</i>		
Musculoskeletal pain (muscle spasm, myalgia, bone pain, arthralgia and pain in extremity).	—	—
Vascular disorder		
<i>Common:</i>		
Venous thromboembolism (VTE)	2.7%	1.9%
General disorders and administration site conditions		
<i>Frequency unknown:^a</i>		
Peripheral oedema	—	—
Pyrexia (in association with hypersensitivity skin reactions)	—	—
Psychiatric disorders		
<i>Frequency unknown:^a</i>		
Confusional state	—	—
Respiratory, thoracic and mediastinal disorders		
<i>Frequency unknown:^a</i>		
Bronchial hyperreactivity	—	—

Investigation Common: Blood Creatinine Kinase (CK) increased ^b	1.4%	0.6%
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^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

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 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

	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

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. Store at room temperature (<30°C).

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.

Registration Number: 142 09 31882

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LICENSE HOLDER: Medilife Ltd., 22 Ben Gurion St., Herzliya

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