

# PROTOS®

## Product Information

PROTOS should only be used when other medications for the treatment for osteoporosis are considered unsuitable. PROTOS is contraindicated and must not be used in patients with established, current or past history of: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, uncontrolled hypertension, venous thromboembolism, pulmonary embolism. It should also not be used in patients who are temporarily or permanently immobilised. PROTOS should be used with caution in patients with risk factors for cardiovascular events or venous thrombosis: hypertension, diabetes, smoking, hyperlipidaemia. All patients prescribed PROTOS should be fully informed of the risk of cardiovascular events and venous thrombosis. Patients should be regularly monitored, every 6 months.

### NAME OF THE MEDICINE

PROTOS®  
strontium ranelate 2 g

### DESCRIPTION

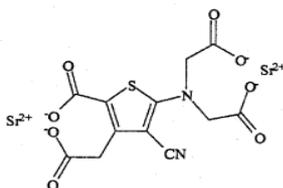
Description of substance and solubility: Strontium ranelate is a yellowish-white non-hygroscopic powder. It crystallises as a nonhydrate form but one water molecule is particularly labile and this leads to a compound containing either 8 or 9 water molecules per strontium ranelate molecule. Strontium ranelate is slightly soluble in purified water (3.7 mg/mL at saturation point) and practically insoluble in organic solvents (e.g. methanol).

*Chemical name:* strontium ranelate

*CAS Registry Number:* 135459-90-4

*Molecular formula:* C<sub>12</sub>H<sub>6</sub>N<sub>2</sub>O<sub>8</sub>SSr<sub>2</sub>

*Chemical structure:*



Excipients:

Aspartame (E951, a source of phenylalanine), maltodextrin, mannitol.

### PHARMACOLOGY

Strontium ranelate has a dual effect on bone metabolism. *In vitro* it increases bone formation by increasing osteoblast precursor replication and collagen synthesis, and reduces bone resorption by altering osteoclast ultrastructure and decreasing resorbing activity in bone cell culture. The activity of strontium ranelate on both long bones and vertebral bodies was studied in various animal

models. Strontium ranelate generally increased bone formation and decreased bone resorption and improved bone biomechanical properties such as bone strength.

In bone tissue, strontium is adsorbed onto the crystal surface and substitutes for calcium in the apatite crystal of the newly formed bone, up to a ratio of 1 strontium atom to 10 calcium atoms. Strontium ranelate does not modify the crystal characteristics. In animals, strontium was progressively eliminated from the bone tissue after treatment withdrawal.

In phase III studies, as compared to placebo, biochemical markers of bone formation (bone-specific alkaline phosphatase) 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. These results confirm the dual mode of action of strontium ranelate on bone cells. In relation to the pharmacological effects of strontium ranelate, slight decreases in calcium and PTH serum levels, increases in blood phosphorus and in total alkaline phosphatase levels were observed, with no clinical consequences.

In human biopsies, the new bone formed with PROTOS treatment has normal mineralisation; in particular, no osteomalacia was observed.

### **Pharmacokinetics**

Strontium ranelate is made up of two atoms of stable strontium and one molecule of ranelic acid, the organic part permitting the best compromise in terms of molecular weight, pharmacokinetics and acceptability of the molecule. 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 20-25 % after an oral dose of 2 g strontium ranelate. Steady state is reached after two weeks of treatment. Intake of strontium ranelate with calcium or food reduces the bioavailability of strontium (see Drug Interactions). 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.

### **Metabolism**

As a divalent cation, strontium is not metabolised. Strontium ranelate does not inhibit cytochrome P<sub>450</sub> enzymes.

### **Excretion**

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 and its renal clearance about 7 mL/min.

### **Special Populations**

In elderly and very elderly patients, no dosage adjustment is required.

In patients with severe renal impairment, in the absence of specific clinical data, PROTOS is contraindicated.

In patients with mild to moderate renal impairment, no dosage adjustment is required. Although strontium plasma levels tend to increase in these patients, the safety profile of PROTOS in phase III studies was similar regardless of whether the patients had a creatinine clearance below or above 30 mL/min at inclusion.

### **Preclinical Safety Data**

Chronic oral administration of strontium ranelate at high doses in rodents induced bone and tooth abnormalities, including spontaneous fractures, joined vertebrae and delayed mineralisation. Complete mineralisation of bone tissue occurred after cessation of treatment. These effects were observed at  $\geq 600$  mg/kg/day in mice and  $\geq 625$  mg/kg/day in rats (where 77 mg/kg/day and 200 mg/kg/day is the minimum effective dose that increases bone volume in rats and mice respectively) with bone strontium levels ca 4 %. These effects were reported at bone strontium levels 2-3 times higher than bone strontium levels in humans exposed to up to 3 years of treatment. The data on skeletal strontium ranelate accumulation in humans following longer term exposure is limited. Osteodystrophy was also observed in mice at very high doses i.e. 7,500 mg/kg/day. (The therapeutic dose of strontium ranelate in humans is 33.3 mg/kg/day).

Urinary bladder calculi associated with hyperplasia have been observed in one species (mice), and not in other species (rats or monkeys).

## **CLINICAL TRIALS**

### **Treatment of Postmenopausal Osteoporosis**

At menopause, acceleration of bone turnover leads to a decrease in bone mass and bone mineral density (BMD), leading to bone fragility. In some women, this results in postmenopausal osteoporosis. The clinical consequence of osteoporosis is a high risk of fracture. The risk of fracture increases with the number of risk factors. These include early menopause, personal history of fracture, family history of osteoporosis, low body weight, smoking, and factors that may favour falls.

In postmenopausal women with osteoporosis, PROTOS reduces the incidence of fractures (both vertebral and non-vertebral), and increases bone mass and BMD. The anti-fracture studies program of PROTOS was made up of two international randomised placebo-controlled phase III studies: the Spinal Osteoporosis Therapeutic Intervention (SOTI) study and the Treatment of Peripheral Osteoporosis (TROPOS) study. In addition to their treatment (2 g/day strontium ranelate or placebo), the patients received calcium and vitamin D supplements throughout both studies. The following clinical trial results for SOTI and TROPOS are based on 3 years.

The SOTI study involved 1,649 postmenopausal women with established osteoporosis (low lumbar BMD and prevalent vertebral fracture) and a mean age of 70 years. The primary efficacy endpoint of this study was the reduction over time in the incidence of a new vertebral fracture in osteoporotic postmenopausal women. The study compared the efficacy of strontium ranelate 2 g/day with placebo.

Patients included in the study had mean menopause duration of  $22 \pm 9$  years, and had a mean lumbar BMD T-score of  $-3.6 \pm 1.3$  (T-scores were calculated according to the reference population

used in the study, Slosman D.O 1994). 83 % of patients had a lumbar BMD T-score  $\leq -2.5$  (Slosman D.O 1994). In patients treated with PROTOS over 3 years, there was a statistically significant reduction in the risk of experiencing a new vertebral fracture (see Table 1).

**Table 1: SOTI -Incidence of patients with new vertebral fracture**

	<b>PROTOS N=719</b>	<b>Placebo N=723</b>	<b>Number Needed to Treat (NNT), (95%CI)</b>	<b>Relative Risk Reduction vs. placebo (95%CI), p value</b>
<b>New vertebral fracture over 3 years</b>	20.9 %	32.8 %	9 (6-14)	41 % (27-52), p< 0.001
<b>New vertebral fracture over the 1<sup>st</sup> year</b>	6.1 %	11.8 %	18 (11-37)	49 % (26-64), p< 0.001
<b>New clinical vertebral fracture over 3 years</b>	11.3 %	17.4 %	16 (10-43)	38 % (17-53), p< 0.001

The TROPOS study involved 5,091 postmenopausal women with mean menopause duration of 28  $\pm$  7 years and a mean age of 77 years. Patients had osteoporosis (low femoral neck BMD) and more than half had at least one prevalent osteoporosis-related fracture. The primary efficacy endpoint of this study was the reduction over time in the incidence of an osteoporosis-related peripheral fracture in osteoporotic postmenopausal women. The study compared the efficacy of strontium ranelate 2 g/day with placebo.

The study population had a mean femoral neck BMD T-score of  $-3.1 \pm 0.6$  (Slosman D.O 1994), and 89 % of patients had a femoral neck BMD T-score  $\leq -2.5$  (Slosman D.O 1994). In patients treated with PROTOS over three years, there was a statistically significant reduction in the risk of experiencing a non-vertebral fracture (see Table 2).

**Table 2: TROPOS -Incidence of patients with non-vertebral fracture**

	<b>PROTOS N=2,479</b>	<b>Placebo N=2,453</b>	<b>Number Needed to Treat (NNT), (95%CI)</b>	<b>Relative Risk Reduction vs. placebo (95%CI), p value</b>
<b>Patients with <math>\geq 1</math> osteoporosis-related peripheral fracture</b>	11.2 %	12.9 %	58 (28-286)	16 % <sup>(1)</sup> (0-29) p=0.044 <sup>(2)</sup>
<b>Patients with major (including hip) osteoporosis-related</b>	8.7 %	10.4 %	59 (28-520)	19 % (2-34) p=0.031

peripheral fracture

(1) Adjustment for covariates (age in classes: < 75 and ≥ 75 years, femoral neck BMD, BMI in classes: ≤ 18, [18-30] and > 30 kg/m<sup>2</sup>, and country) (2) According to substitution rules for covariates.

In patients over 80 years of age at inclusion, a pooled analysis of SOTI and TROPOS studies showed that there was a statistically significant reduction in the risk of experiencing both new vertebral and non-vertebral fractures over three years of treatment with PROTOS (see Table 3).

The pooled analysis of SOTI and TROPOS also showed a statistically significant reduction in the relative risk of experiencing a new vertebral fracture in patients with osteopenia (defined according to WHO criteria as patients with lumbar and/or femoral neck BMD T-score ≤ -1SD and both T-scores > -2.5SD) (see Table 3).

**Table 3. Integrated Analysis of Efficacy for SOTI and TROPOS studies**

	PROTOS	Placebo	Number Needed to Treat (NNT), (95%CI)	Relative Risk Reduction vs. placebo (95%CI), p value
<b>Main Results</b>				
<b>Osteoporosis-related peripheral fractures</b>	<b>N=3,295</b> 11.6 %	<b>N=3,256</b> 13.1 %	67 (30-331)	15 % (1-26) p= 0.033
<b>Any osteoporosis-related fractures</b>	21.1 %	29.1 %	13 (10-17)	31 % (23-38) p< 0.001
<b>Any clinical osteoporosis-related fractures</b>	16.6 %	20.0 %	29 (18-72)	20% (10-29) p< 0.001
<b>Patients older than 80 years</b>				
<b>Osteoporosis-related peripheral fractures</b>	<b>N=739</b> 14.2 %	<b>N=749</b> 19.7 %	18 (10-126)	31 % (8-48) p= 0.011
<b>Vertebral fractures</b>	<b>n=443</b> 19.1 %	<b>n=452</b> 26.5 %	13 (7-80)	32 % (8-50) p= 0.013
<b>Patients with Osteopenia</b>				
<b>Vertebral fractures</b>	<b>N=206</b> 8.1 %	<b>N=203</b> 18.6 %	10 (6-28)	62 % (30-79) p= 0.001

**Treatment of Osteoporosis in men**

The efficacy of PROTOS was demonstrated in men with osteoporosis in a double-blind, placebo-controlled study with the primary analysis at one year, in patients at high risk of fracture. The intention to treat (ITT) population comprised 243 patients, of which 161 received strontium ranelate 2 g/day. Patients had a mean age of 72.7 years and a mean lumbar BMD T-score value of -2.6. Twenty-eight per cent had a prevalent vertebral fracture.

All patients received daily supplemental calcium (1000 mg) and vitamin D (800 IU). The primary efficacy endpoint was the percentage change from baseline to end of lumbar L2-L4 BMD. Statistically significant increases in BMD were observed as early as six months following initiation of PROTOS treatment versus placebo.

Over 12 months, a statistically significant increase in mean lumbar spine BMD, main efficacy criteria ( $p < 0.001$ ), similar to that observed in the pivotal anti-fracture phase III studies carried-out in postmenopausal women, was observed.

Statistically significant increases in femoral neck BMD and total hip BMD ( $p < 0.001$ ) were also observed.

Osteoporosis was confirmed by the finding of low bone mass of at least 2.5 standard deviations below the gender specific mean for young adults, or by the presence of osteoporotic fracture.

## **INDICATIONS**

Treatment of severe (established) osteoporosis:

- in postmenopausal women at high risk of fracture to reduce the risk of fracture.
- in men at increased risk of fracture

PROTOS should only be used when other medications for the treatment for osteoporosis are considered unsuitable (due to contraindications or intolerance).

## **CONTRAINDICATIONS**

- History of ischaemic heart disease, peripheral arterial disease or cerebrovascular disease
- Systolic blood pressure (SBP) greater than or equal to 160 mmHg, or diastolic blood pressure (DBP) greater than or equal to 90 mmHg.
- Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.
- Temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest).
- Severe renal impairment (see *Pharmacokinetics–Special Populations* section)
- Known hypersensitivity to strontium ranelate or to any of the excipients

## **PRECAUTIONS**

Treatment should only be initiated by a doctor with experience in treating osteoporosis. The decision to prescribe PROTOS should be based on an assessment of the individual patient's overall risks (see *CONTRAINDICATIONS* and *PRECAUTIONS* sections).

Patients should be evaluated for cardiovascular risk prior to commencement of PROTOS and during ongoing treatment (see *PRECAUTIONS-Cardiac ischaemic events* section).

Calcium and vitamin D deficiencies occur frequently in the elderly, particularly in the institutionalised or those who avoid direct sun exposure. Patients should receive vitamin D and calcium supplements if dietary intake is inadequate.

All men with osteoporosis should be investigated for secondary osteoporosis e.g. hypogonadism and, if necessary, treated for that condition.

### Cardiac ischaemic events

In pooled randomised placebo-controlled studies of patients with post-menopausal osteoporosis, a significant increase in myocardial infarction has been observed in PROTOS treated patients compared to placebo (see *ADVERSE EFFECTS* section).

Patients should be evaluated for cardiovascular risk prior to commencement of PROTOS and during ongoing treatment on a regular basis generally every 6 months. All patients should be fully informed of this regular monitoring. Patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with PROTOS after careful consideration (see *ADVERSE EFFECTS* and *CONTRAINDICATIONS* sections).

Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if SBP is greater than or equal to 160 mmHg, or DBP is greater than or equal to 90 mmHg (see *CONTRAINDICATIONS* section).

### **Venous thromboembolism**

In phase III placebo controlled studies, strontium ranelate treatment was associated with an increase in the annual incidence of VTE, including pulmonary embolism (see *ADVERSE EFFECTS* section). The cause of this finding is unknown.

PROTOS is contraindicated in patients with a past history of venous thromboembolic events (see *CONTRAINDICATIONS* section) and should be used with caution in patients at risk of VTE. In patients over 80 years at risk of VTE, ongoing treatment with PROTOS should be re-evaluated.

In the event of an illness or a condition leading to immobilisation (see *CONTRAINDICATIONS* section), PROTOS should be discontinued as soon as possible and adequate preventive measures taken. Therapy should not be restarted until the event has resolved and the patient is mobile. PROTOS should be stopped if VTE occurs.

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

Treatment with PROTOS should be discontinued in case of allergic reaction to strontium ranelate or to any of the excipients.

### **Use in patients with renal impairment**

PROTOS is contraindicated in patients with severe renal impairment (see *CONTRAINDICATIONS*, *PHARMACOKINETICS-Special Population* sections). In accordance with good medical practice, periodic assessment of renal function is recommended in patients with chronic renal impairment.

### **Hypersensitivity reactions**

Cases of 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 PROTOS.

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, PROTOS treatment should be discontinued immediately.

Early diagnosis and immediate discontinuation of the suspected drug is associated with a better prognosis of SJS, TEN or DRESS. In cases of DRESS consider initiation of corticosteroid therapy following discontinuation of PROTOS. Recovery from DRESS could be slow and recurrences have been reported in some cases after discontinuation of corticosteroid therapy.

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

A higher incidence of hypersensitivity reactions including skin rash, SJS or TEN has been reported in Asian patients with HLA types A\*33:03 and HLA B\*58:01 (see *ADVERSE EFFECTS* section).

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 PROTOS in patients of Han Chinese origin. If tests are positive for one or both alleles, PROTOS should not be started. However, absence of these alleles upon genotyping does not exclude that SJS/TEN can still occur.

### **Effects on Fertility**

Male and Female fertility in rats were unaffected by strontium ranelate treatment (1000 mg/kg/day, with plasma AUC values for strontium similar to the average clinical value).

### **Use in Pregnancy - Category B3**

PROTOS is intended for use in postmenopausal women.

No clinical data on exposed pregnancies are available for strontium ranelate. Animal reproductive studies showed bone abnormalities (e.g. bent bones, wavy ribs, arthrogryposis) of the foetus from pregnant rats and rabbits at oral doses  $\geq$  500 mg/kg/day, which results in plasma AUC values for strontium and ranelic acid lower than or similar to the average clinical value. These effects were reversible eight weeks after cessation of treatment. If women taking PROTOS become pregnant, they should stop taking it immediately.

### **Use in Lactation**

Strontium accumulates in rat milk, giving milk/plasma ratios up to 73 at an oral dose of 750 mg/kg/day strontium ranelate. High levels of strontium were detected in the plasma of suckling neonates of lactating rats treated with strontium ranelate. Strontium ranelate treatment of lactating rats delayed incisor eruption of the offspring. PROTOS should not be given to breast-feeding women.

### **Paediatric Use**

Use not recommended, as no data are available in children.

### **Genotoxicity**

Strontium ranelate was non-genotoxic in a battery of assays including *in vitro* bacterial gene mutation (*Salmonella typhimurium* and *E. coli*), *in vitro* mammalian cell gene mutation (Chinese hamster fibroblast cells), *in vitro* chromosome aberration (human lymphocytes), *in vitro* unscheduled DNA synthesis in rat hepatocytes, and *in vivo* bone marrow micronucleus formation in rodents.

### **Carcinogenicity**

Long-term studies with strontium ranelate at oral doses (in the diet) up to 1,800 mg/kg/day in mice and 625/900 (male/female) mg/kg/day in rats showed no treatment-related increase in the incidence of tumours. These doses resulted in plasma strontium and ranelic acid AUC values approximately 2 and 4-6 times the average clinical value, respectively.

### **Effects on Ability to Drive and Use Machines**

There are no data to suggest that PROTOS affects the ability to drive or use machines.

## **INTERACTIONS WITH OTHER MEDICINES**

Food, milk and derivative products, and medicines containing calcium may reduce the bioavailability of strontium ranelate by approximately 60-70 %. Therefore, PROTOS should preferably be taken at least two hours after such products (see *PHARMACOLOGY-Pharmacokinetics* section).

As divalent cations form a complex with oral tetracycline (e.g. doxycycline) and quinolone antibiotics (e.g. ciprofloxacin) at the gastro-intestinal level, thus reducing their absorption, simultaneous administration of strontium ranelate with these drugs is not recommended. As a precautionary measure, PROTOS treatment should be suspended during treatment with oral tetracycline or quinolone antibiotics and reintroduced the day following the last antibiotic dose.

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 PROTOS. However, when this dosing regimen is impractical due to the recommend administration of PROTOS at bedtime, concomitant intake remains acceptable.

Strontium ranelate is not metabolised, does not inhibit cytochrome P<sub>450</sub> enzymes and has low protein binding. As a consequence, PROTOS is not expected to interact with other medicinal products.

No interaction was observed with oral supplementation of vitamin D.

There are no clinical data concerning the concomitant medication with one or more bisphosphonates and such concomitant medication is not recommended.

### **Effects on Laboratory Tests**

Strontium interferes with colorimetric methods for the determination of blood and urinary calcium levels. 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 levels.

The combined effects of the atomic weight and increased X-ray absorption of strontium as compared to calcium, lead 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 PROTOS 2 g/day. This should be taken into account when interpreting BMD changes during treatment with PROTOS.

## **ADVERSE EFFECTS**

Summary of cardiovascular and venous thromboembolic risks

Data from randomised controlled trials show that PROTOS is associated with an increased risk of myocardial infarction and venous thromboembolism.

In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in PROTOS treated patients as compared to placebo (5.7 per 1,000 patient-years versus 3.6 per 1,000 patients-years), with a relative risk of 1.6 (95% CI = [1.07 ; 2.38]).

In phase III studies, venous thromboembolism occurred in 2.7 % of patients in the strontium group and 1.9 % of patients in the placebo group; relative risk: 1.4 (95% CI = [1.0 ; 2.0]).

**Extent of safety data**

PROTOS 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 5 years with PROTOS (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.

Overall incidence rates for adverse events with strontium ranelate did not differ from placebo group and adverse events were usually mild and transient. The most common adverse events 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).

There were no differences in the nature and frequency of adverse events between treatment groups regardless of whether patients were aged below or above 80 at inclusion.

The following adverse reactions have been reported during clinical studies with strontium ranelate.

Adverse reactions are 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).

<b><u>System Organ Class (SOC)</u></b> <b>Frequency category</b> <b>Adverse Drug Reaction</b>	<b>Patients Experiencing the ADR (%)</b>	
	<b>Strontium ranelate (n=3,352)</b>	<b>Placebo (n=3,317)</b>
<b><u>Nervous system disorders</u></b>		
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
<b><u>Cardiac disorders</u></b>		
Common <sup>b</sup> :		
Myocardial infarction	1.7	1.1
<b><u>Gastrointestinal disorders</u></b>		
Common:		
Nausea	7.1	4.6
Diarrhoea	7.0	5.0
Loose stools	1.0	0.2
<b><u>Skin and subcutaneous tissue disorders</u></b>		
Common:		
Dermatitis	2.3	2.0
Eczema	1.8	1.4
<b><u>Vascular disorders</u></b>		
Common:		
Venous thromboembolism (VTE)	2.7	1.9
<b><u>Investigations</u></b>		
Common:		
Blood Creatine phosphokinase (CPK) increase <sup>a</sup>	1.4	0.6

<sup>a</sup> 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.

<sup>b</sup> In pooled placebo-controlled studies of patients with post-menopausal osteoporosis, strontium ranelate treated patients (N=3,803, 11,270 patient years of treatment) compared to placebo (N=3,769, 11,250 patient years of treatment)

## **Post Marketing Experience**

The following adverse reactions have been reported in post-marketing use of strontium ranelate. The frequency of these reactions is calculated from adverse events detected in clinical trials, except where stated otherwise.

### **Blood and Lymphatic system disorders**

*Uncommon:* lymphadenopathy (in association with hypersensitivity skin reactions)

*Rare:* bone marrow failure<sup>#</sup>, eosinophilia (in association with hypersensitivity skin reactions)

### **Metabolism and nutrition disorders**

*Common:* hypercholesterolaemia

### **Psychiatric disorders**

*Common:* insomnia

*Uncommon:* confusion

### **Nervous system disorders**

*Common:* paraesthesia, dizziness

### **Ear and labyrinth disorders**

*Common:* vertigo

### **Respiratory, thoracic and mediastinal disorders**

*Common:* bronchial hyperreactivity

### **Gastrointestinal disorders**

*Common:* vomiting, abdominal pain, gastro-intestinal pain, dyspepsia, gastro-oesophageal reflux, constipation, flatulence

*Uncommon:* oral mucosal irritation including; stomatitis and/or mouth ulceration, dry mouth

### **Hepatobiliary disorders**

*Common:* hepatitis

*Uncommon:* serum transaminase increase (in association with hypersensitivity skin reactions)

### **Skin and subcutaneous tissue disorders**

*Very common:* hypersensitivity skin reactions including rash, pruritus, urticaria, angioedema<sup>§</sup>

*Uncommon:* alopecia

*Rare:* cases of severe hypersensitivity syndromes including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)<sup>#</sup> (see *PRECAUTIONS* section)

*Very rare:* Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)<sup>#</sup> (see *PRECAUTIONS* section). A higher incidence (although rare) of hypersensitivity reactions including skin rash, SJS or TEN has been reported in patients of Asian origin.

### **Musculoskeletal and connective tissue disorders**

*Very common:* musculoskeletal pain including muscle spasm, myalgia, bone pain, arthralgia and pain in extremities<sup>§</sup>

<sup>§</sup> Frequency in clinical trials was similar in the strontium ranelate and placebo group.

<sup>#</sup> 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 number of patients from all relevant clinical trials and studies.

General disorders and administration site conditions

*Common:* peripheral oedema

*Uncommon:* pyrexia (in association with hypersensitivity skin reactions), malaise

Laboratory Findings

Blood creatine phosphokinase (CPK) was systematically assessed at each visit in phase III studies. Without it having been associated with clinical muscular symptoms or other biological abnormalities, transient emergent increases (> 3 times the upper limit of the normal range) in CPK (musculo-skeletal fraction) were reported in 1.4 % and 0.6 % of the strontium ranelate and placebo groups respectively. These values spontaneously normalised with no treatment change.

**DOSAGE AND ADMINISTRATION**

Treatment should only be initiated by a doctor with experience in treating osteoporosis (see PRECAUTIONS section).

The recommended daily dose for the treatment of osteoporosis is one 2 g sachet once daily by oral administration (see CLINICAL TRIALS section).

Due to the nature of this disease, PROTOS is intended for long-term use (see *ADVERSE EFFECTS* section). As with all chronic diseases, the management of osteoporosis should be reviewed on a regular basis and current practice guidelines should be consulted.

**Method of Administration**

Patients should preferably take PROTOS at bedtime since the absorption of strontium ranelate may be affected by food intake (see Drug Interactions and Pharmacokinetics). PROTOS can be taken on an empty stomach.

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 preparation.

**Use in the Elderly**

The efficacy and safety of PROTOS have been established in a broad age range (up to 100 years at inclusion) of adult men and postmenopausal women with osteoporosis. No dosage adjustment is required in relation to age, even in the very elderly.

**Use in Renal Impairment**

No dosage adjustment is required in patients with mild to moderate renal impairment. PROTOS is contraindicated in patients with severe renal impairment (see *CONTRAINDICATIONS* and *Pharmacokinetics–Special Populations* sections).

**Use in Hepatic Impairment**

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

## **OVERDOSAGE**

**Advice on overdose management can be obtained from the national Poisons Information Centre by telephoning 131126.**

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 drug. In the event of substantial overdose, vomiting may be considered to remove unabsorbed drug.

## **PRESENTATION**

Granules for oral suspension. PROTOS 2 g sachets contain 2 g strontium ranelate as a yellow powder. Boxes contain 7 or 28 sachets (paper/polyethylene/aluminium/ polyethylene sachets).

## **STORAGE**

Store in a dry place below 30 °C.

Shelf life: 3 years in original packaging. 24 hours after suspension in drinking water.

## **POISONS SCHEDULE OF THE MEDICINE**

S4 - Prescription Only Medicine

## **NAME AND ADDRESS OF THE SPONSOR**

Servier laboratories (Aust.) Pty Ltd  
8 Cato Street,  
Hawthorn, Victoria 3122  
Australia  
ABN 54 004 838 500

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Level 4, Zurich House  
21 Queen Street  
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Auckland 1010

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

21 June 2005

## **DATE OF MOST RECENT AMENDMENT**

01 August 2017