

Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.

# PROTOS<sup>®</sup>

## NAME OF THE DRUG

**PROTOS<sup>®</sup>**

strontium ranelate 2g

## DESCRIPTION

Description of substance and solubility: Strontium ranelate is a yellowish-white non-hygroscopic powder. It crystallises as a nonahydrate 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 (3.7mg/mL at saturation point) and practically insoluble in organic solvents (eg, methanol).

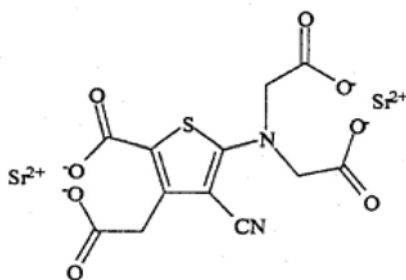
*Excipients:* Aspartame (E951, a source of phenylalanine), maltodextrin, mannitol.

*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:



## 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.

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

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 is normal (i.e., lamellar) and of good quality with normal mineralisation; in particular, no osteomalacia was observed.

### **Pharmacokinetics and Metabolism**

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 2g 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 1L/kg. The binding of strontium to human plasma proteins is low (25%) and strontium has a high affinity for bone tissue. There is no accumulation of strontium in non-calcified tissues.

#### **Biotransformation**

As a divalent cation, strontium is not metabolised. Strontium ranelate does not inhibit cytochrome P<sub>450</sub> 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 12mL/min and its renal clearance about 7mL/min.

#### **Special Populations**

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

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

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 30mL/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. These effects were observed at  $\geq 600\text{mg/kg/day}$  in mice and  $\geq 625\text{mg/kg/day}$  in rats (where  $77\text{mg/kg/day}$  and  $200\text{mg/kg/day}$  is the minimum effective dose that increases bone volume in rats and mice respectively) with bone strontium levels *ca* 4%. Complete mineralisation of bone tissue occurred after cessation of treatment. Osteodystrophy was also observed in mice at very high doses i.e.  $7500\text{mg/kg/day}$ . (The therapeutic dose of strontium ranelate in humans is  $33.3\text{mg/kg/day}$ ).

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 ( $2\text{g/day}$  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 three 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  $2\text{g/day}$  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-

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

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 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 2g/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).

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

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

	<b>PROTOS</b> <b>N=2479</b>	<b>Placebo</b> <b>N=2453</b>	<b>Number Needed to Treat (NNT), (95%CI)</b>	<b>Relative Risk Reduction vs. placebo (95%CI), p value</b>
<b>Patients with ≥1 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 peripheral fracture</b>	8.7%	10.4%	59 (28-520)	19% (2-34) p=0.031

(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).

Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.

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>N=3295</b>	<b>N=3256</b>		
<b>Osteoporosis-related peripheral fractures</b>	11.6%	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>N=739</b>	<b>N=749</b>		
<b>Osteoporosis-related peripheral fractures</b>	14.2%	19.7%	18 (10-126)	31% (8-48) p=0.011
	<b>n=443</b>	<b>n=452</b>		
<b>Vertebral fractures</b>	19.1%	26.5%	13 (7-80)	32% (8-50) p=0.013
<b>Patients with Osteopenia</b>				
	<b>N=206</b>	<b>N=203</b>		
<b>Vertebral fractures</b>	8.1%	18.6%	10 (6-28)	62% (30-79) p=0.001

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

## 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 2g/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 6 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 postmenopausal osteoporosis to reduce the risk of fracture.

Treatment of osteoporosis in men at increased risk of fracture.

## CONTRAINDICATIONS

- Known hypersensitivity to strontium ranelate or to any of the excipients
- Severe renal impairment (see Pharmacokinetics – Special Populations)
- 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).

## PRECAUTIONS

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.

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

### **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 Adverse Reactions section). The cause of this finding is unknown.

PROTOS is contraindicated in patients with a past history of venous thromboembolic events (see CONTRAINDICATIONS) 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), 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.

### **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.

### **Carcinogenicity**

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*



**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

*vitro* unscheduled DNA synthesis in rat hepatocytes, and *in vivo* bone marrow micronucleus formation in rodents.

### **Mutagenicity**

Long-term studies with strontium ranelate at oral doses (in the diet) up to 1800 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 Fertility**

Male and Female fertility in rats were unaffected by strontium ranelate treatment (1000mg/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 (eg. bent bones, wavy ribs, arthrogyrosis) of the foetus from pregnant rats and rabbits at oral doses  $\geq$  500mg/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 750mg/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.

### **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. Therefore, PROTOS should preferably be taken at least two hours after such products (see Pharmacokinetics).

As divalent cations form a complex with oral tetracycline and quinolone antibiotics at the gastro-intestinal level, thus reducing their absorption, simultaneous administration of strontium ranelate with these drugs is not recommended. As a precautionary measure,

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

PROTOS treatment should be suspended during treatment with oral tetracycline or quinolone antibiotics and reintroduced the day following the last antibiotic dose.

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 2g/day. This should be taken into account when interpreting BMD changes during treatment with PROTOS.

**ADVERSE REACTIONS**

Safety data in humans is currently available for 8 years.

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 rate 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).

In an extension study, osteoporotic women who received PROTOS during a 5-year period in phase III studies, were treated with the drug for an additional 3 years. The frequencies of undesirable effects associated with the use of strontium ranelate during years 6-8 of PROTOS treatment were lower than those in years 0-3.

The undesirable effects associated with the use of strontium ranelate in phase III studies over an 8-year period, are the following (frequencies versus placebo):

	<b>Years 0-3</b>	<b>Years 0-5</b>	<b>Years 6-8*</b>
--	------------------	------------------	-------------------

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

<b>Nausea</b>	6.6% v 4.3%	7.1% v 4.6%	0.9% v na
<b>Diarrhoea</b>	6.5% v 4.6%	7.0% v 5.0%	2.7% v na
<b>Headache</b>	3.0% v 2.4%	3.3% v 2.7%	0.7% v na
<b>Dermatitis</b>	2.1% v 1.6%	2.3% v 2.0%	<1.0% v na
<b>Eczema</b>	1.5% v 1.2%	1.8% v 1.4%	<1.0% v na
<b>Loose stools</b>	1.1% v 0.2%	1.0% v 0.2%	0.1% v na

\*Incidence rates are not versus placebo as all women included in the 3-year extension study were treated with PROTOS (i.e. no placebo arm).

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.

During phase III studies, the observed annual incidences of venous thromboembolism (VTE) were 0.9% and 0.6% in strontium ranelate and placebo groups respectively. These incidences were consistent with that expected in the age range of the studied population. Despite the increasing age of patients treated with PROTOS in the 3-year extension study, the incidence of VTE remained unchanged.

Adequate prevention measures should be taken in patients encountering high-risk of VTE (see PRECAUTIONS).

The following adverse reactions have been reported during clinical studies 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: 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).

<b>System Organ Class (SOC)</b>	<b>Patients Experiencing the ADR</b>	
	<b>(%)</b>	
<b>Frequency category</b>	<b>Strontium ranelate</b>	<b>Placebo</b>
<b>Adverse Drug Reaction</b>	<b>(n=3352)</b>	<b>(n=3317)</b>
<b>Nervous system disorders</b>		
<i>Common:</i>		
Headache	3.3	2.7
Disturbances in consciousness	2.6	2.1

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

Memory loss	2.5	2.0
<i>Uncommon:</i>		
Seizures	0.4	0.1
<b>Gastrointestinal disorders</b>		
<i>Common:</i>		
Nausea	7.1	4.6
Diarrhoea	7.0	5.0
Loose stools	1.0	0.2
<b>Skin and subcutaneous tissue disorders</b>		
<i>Common:</i>		
Dermatitis	2.3	2.0
Eczema	1.8	1.4
<b>Vascular disorders</b>		
<i>Common:</i>		
Venous thromboembolism (VTE)	2.7	1.9
<b>Investigations</b>		
<i>Common:</i>		
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.

### **Post Marketing Experience**

The following adverse reactions have been reported in post-marketing use with strontium ranelate. The frequency of these events is unknown.

#### **Gastrointestinal disorders:**

Vomiting, abdominal pain, oral mucosal irritation including; stomatitis and/or mouth ulceration, dyspepsia, gastro-oesophageal reflux, constipation, flatulence

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

Musculoskeletal and connective tissue disorders

Musculoskeletal pain including muscle spasm, myalgia, bone pain, arthralgia and pain in extremities

Skin and subcutaneous tissue disorders:

Unknown: Hypersensitivity skin reactions including rash, pruritus, urticaria, angioedema, alopecia

Rare: Cases of severe hypersensitivity syndromes including drug rash with eosinophilia and systemic symptoms (DRESS) (see PRECAUTIONS)

Very rare: Severe cutaneous adverse reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see PRECAUTIONS)

Blood and Lymphatic system disorders:

Bone marrow failure, eosinophilia (in association with hypersensitivity skin reactions), lymphadenopathy (in association with hypersensitivity skin reactions)

Hepatobiliary disorders:

Serum transaminase increase (in association with hypersensitivity skin reactions), hepatitis

General disorders and administration site conditions:

Peripheral oedema, pyrexia (in association with hypersensitivity skin reactions)

Respiratory, thoracic and mediastinal disorders:

Bronchial hyperreactivity Psychiatric disorders:

Confusional state, insomnia

**Laboratory Findings**

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**

The recommended daily dose for the treatment of osteoporosis is one 2g 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 Reactions section). As with all chronic diseases, the management of osteoporosis should be reviewed on a regular basis and current practice guidelines should be consulted.

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

## **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 30ml (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 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).

## **Use in Hepatic Impairment**

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

## **OVERDOSAGE**

Good tolerance was shown in a clinical study investigating the repeated administration of 4g strontium ranelate per day over 25 days in healthy postmenopausal women. Single administration of doses up to 11g in healthy young male volunteers did not cause any particular symptoms.

Following episodes of overdoses during clinical trials (up to 4g/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.

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

## **PRESENTATION**

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

**Attachment 1: Product information for AusPAR Protos Strontium ranelate Servier Laboratories (Australia) Pty Ltd PM-2011-00498-3-5 Final 7 January 2013. This Product Information was approved at the time this AusPAR was published.**

## **STORAGE**

Store in a dry place below 30°C.

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

## **POISONS SCHEDULE**

S4

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

SERVIER LABORATORIES (AUSTRALIA) PTY LTD  
 8 Cato Street,  
 Hawthorn, Victoria 3122  
 Australia  
 ABN 54 004 838 500

SERVIER LABORATORIES (NEW ZEALAND) LTD  
 12th Floor, Citibank Building  
 23 Customs Street  
 Auckland

**AUST R 99978**

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

21 June 2005

### **DATE OF MOST RECENT AMENDMENT**

4 May 2012