

PROTOS[®]

DATA SHEET

NAME OF THE DRUG

PROTOS[®]
strontium ranelate 2g

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 (3.7mg/mL at saturation point) and practically insoluble in organic solvents (eg, methanol).

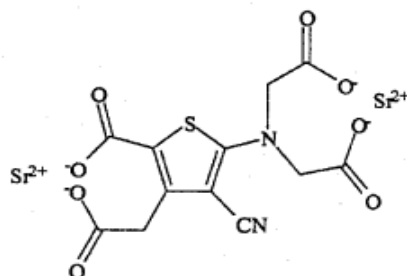
Excipients: Aspartame (E951, a source of phenylalanine), maltodextrin, mannitol.

Chemical name: strontium ranelate

CAS Registry Number: 135459-90-4

Molecular formula: C₁₂H₆N₂O₈SSr₂

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.

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 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 12mL/min and its renal clearance about 7mL/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 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 77mg/kg/day and 200mg/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. 7500mg/kg/day . (The therapeutic dose of strontium ranelate in humans is 33.3mg/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.

Osteoporosis Treatment

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 (2g/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 2g/day with placebo.

Patients included in the study had mean menopause duration of 22±9 years, and had a mean lumbar BMD T-score of -3.6±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 ≤-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

	PROTOS N=719	Placebo N=723	Number Needed to Treat (NNT), (95%CI)	Relative Risk Reduction vs. placebo (95%CI), p value
New vertebral fracture over 3 years	20.9%	32.8%	9 (6-14)	41% (27-52), p<0.001
New vertebral fracture over the 1st year	6.1%	11.8%	18 (11-37)	49% (26-64), p<0.001
New clinical vertebral fracture over 3 years	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±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 ± 0.6 (Slosman D.O 1994), and 89% of patients had a femoral neck BMD T-score ≤ -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

	PROTOS N=2479	Placebo N=2453	Number Needed to Treat (NNT), (95%CI)	Relative Risk Reduction vs. placebo (95%CI), p value
Patients with ≥ 1 osteoporosis-related peripheral fracture	11.2%	12.9%	58 (28-286)	16% ⁽¹⁾ (0-29), p=0.044 ⁽²⁾
Patients with major (including hip) osteoporosis-related peripheral fracture	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/m², 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 ≤ -1 SD and both T-scores > -2.5 SD) (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
Main Results				
	N=3295	N=3256		
Osteoporosis-related peripheral fractures	11.6%	13.1%	67 (30-331)	15% (1-26), p=0.033
Any osteoporosis-related fractures	21.1%	29.1%	13 (10-17)	31% (23-38), p<0.001
Any clinical osteoporosis-related fractures	16.6%	20.0%	29 (18-72)	20% (10-29), p<0.001
Patients older than 80 years				
	N=739	N=749		
Osteoporosis-related peripheral fractures	14.2%	19.7%	18 (10-126)	31% (8-48), p=0.011
	n=443	n=452		
Vertebral fractures	19.1%	26.5%	13 (7-80)	32% (8-50), p=0.013
Patients with Osteopenia				
	N=206	N=203		

Vertebral fractures	8.1%	18.6%	10 (6-28)	62% (30-79), p=0.001
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INDICATIONS

Treatment of postmenopausal osteoporosis to reduce the risk of fracture.

CONTRAINDICATIONS

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

PRECAUTIONS

PROTOS is only intended for use in postmenopausal women.

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.

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 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 measure taken.

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 drug rash with eosinophilia and systemic symptoms (DRESS) also known as drug hypersensitivity syndrome (DHS) have been reported and have sometimes been fatal. This reaction 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. Recovery could be slow and recurrences of the syndrome have been reported in some cases after discontinuation of corticosteroid therapy.

Treatment with PROTOS should be discontinued immediately and permanently when a rash occurs and patients should seek medical advice. Patients who have stopped treatment due to hypersensitivity reactions should not re-start therapy with PROTOS.

Carcinogenicity, Mutagenicity and Impairment of Fertility

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.

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.

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 only 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, arthrogyposis) of the foetus from pregnant rats and rabbits at oral doses $\geq 500\text{mg/kg/day}$, 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 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.

Drug Interactions

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 gastrointestinal 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.

Strontium ranelate is not metabolised, does not inhibit cytochrome P₄₅₀ 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):

	Years 0-3	Years 0-5	Years 6-8*
Nausea	6.6% v 4.3%	7.1% v 4.6%	0.9% v na
Diarrhoea	6.5% v 4.6%	7.0% v 5.0%	2.7% v na
Headache	3.0% v 2.4%	3.3% v 2.7%	0.7% v na
Dermatitis	2.1% v 1.6%	2.3% v 2.0%	<1.0% v na
Eczema	1.5% v 1.2%	1.8% v 1.4%	<1.0% v na
Loose stools	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).

System Organ Class (SOC) Frequency category Adverse Drug Reaction	Patients Experiencing the ADR (%)	
	Strontium ranelate (n=3352)	Placebo (n=3317)

Nervous system disorders <i>Common:</i> Headache Disturbances in consciousness Memory loss <i>Uncommon:</i> Seizures	3.3 2.6 2.5 0.4	2.7 2.1 2.0 0.1
Gastrointestinal disorders <i>Common:</i> Nausea Diarrhoea Loose stools	7.1 7.0 1.0	4.6 5.0 0.2
Skin and subcutaneous tissue disorders <i>Common:</i> Dermatitis Eczema	2.3 1.8	2.0 1.4
Vascular disorders <i>Common:</i> Venous thromboembolism (VTE)	2.7	1.9
Investigations <i>Common:</i> Blood Creatine phosphokinase (CPK) increase ^a	1.4	0.6

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

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

Musculoskeletal and connective tissue disorders

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

Skin and subcutaneous tissue disorders:

Hypersensitivity skin reactions including rash, pruritus, urticaria, angioedema, Stevens-Johnson syndrome. Cases of severe hypersensitivity syndromes including drug rash with eosinophilia and systemic symptoms (DRESS) (see PRECAUTIONS), Toxic epidermal necrolysis, alopecia

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.

Due to the nature of this disease, PROTOS is intended for long-term use (see Adverse Reactions section).

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).

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

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DATE OF PREPARATION

21 November 2011