

Strontium ranelate (Protelos): new option in osteoporosis

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PRODUCT PROFILE

Proprietary name: Protelos

Constituents: strontium ranelate

Indication: treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures

Dosage and method of administration: *adults* – one 2g sachet once daily by oral administration; granules must be taken as a suspension in a glass of water; bioavailability of strontium ranelate is reduced by food and dairy and calcium-containing products and, therefore, it should preferably be taken at bedtime at least two hours after eating; *elderly patients and patients with hepatic impairment and/or mild to moderate renal impairment* – no dosing modification required; *severe renal impairment (creatinine clearance <30ml per minute)* – not recommended; *children and adolescents* – not recommended

Contraindications: patients hypersensitive to strontium ranelate or its excipients

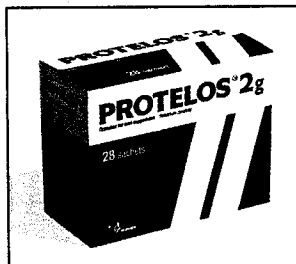
Precautions: monitor renal function in chronic renal impairment; use with caution in patients at risk of venous thromboembolism (a small but significant increase was observed in clinical trials); contains a source of phenylalanine, which may be harmful for people with phenylketonuria

Pregnancy and lactation: only for use in postmenopausal women

Interactions: strontium may reduce absorption of oral tetracycline or quinolone antibiotics – discontinue strontium ranelate during treatment; it is preferable to take antacids at least two hours after strontium ranelate as concomitant intake, though acceptable, may cause a slight decrease in the absorption of strontium

Side-effects: *common:* nausea, diarrhoea, headache, dermatitis, eczema

Presentation/cost: sachets containing 2g strontium ranelate granules for oral suspension; 28 sachets – £25.60



Strontium ranelate (Protelos) is a new treatment for postmenopausal osteoporosis with a novel mode of action. Professor Spector examines the clinical evidence for its efficacy and tolerability and considers how it compares with existing osteoporosis treatments.

Strontium ranelate (Protelos) is a new agent licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fracture. It is the first in a new class of drugs for osteoporosis called Dual Action Bone Agents (DABAs), and it is the first nonbisphosphonate treatment to be licensed for the reduction of hip fractures.

The licensed indication is based on the results of pivotal clinical tri-

als showing that strontium ranelate reduces both vertebral and non-vertebral fractures, including hip fractures, and increases bone mineral density (BMD).^{1,2}

Strontium ranelate 2g is a once-daily treatment, formulated as a powder that is suspended in water, and should be taken at bedtime preferably at least two hours after eating. Co-administration of calcium supplements should also be separated by at least two hours as

calcium reduces the bioavailability of strontium ranelate.

Mechanism of action

Strontium ranelate is a compound of ranelic acid and stable strontium that appears to have a different mode of action to existing drugs for osteoporosis. Bisphosphonates, hormone replacement therapy (HRT) and selective oestrogen receptor modulators (SERMs) reduce bone resorption, while

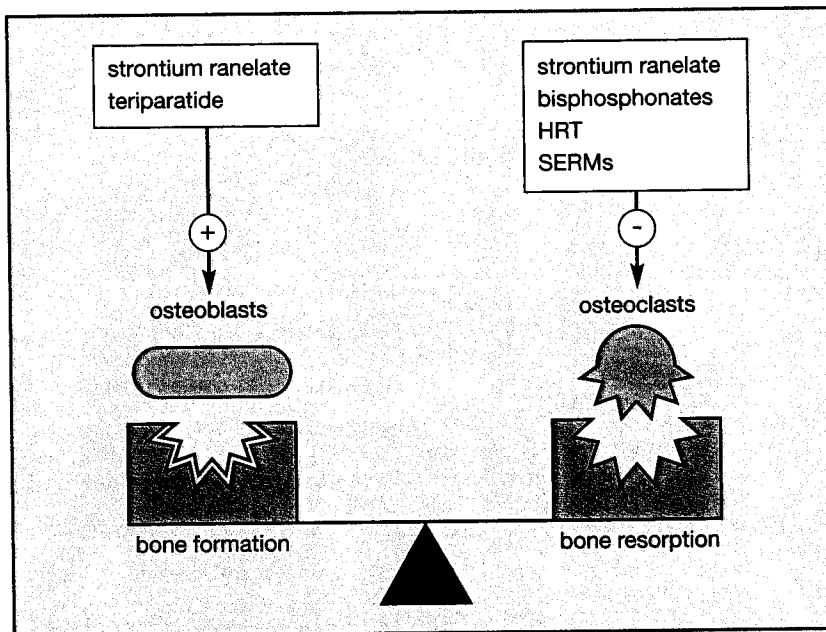


Figure 1. Osteoporosis is caused when bone resorption (osteoclasts) exceeds bone formation (osteoblasts). Strontium ranelate stimulates osteoblast activity and inhibits osteoclast activity

parathyroid hormone – teriparatide (Forsteo) – increases bone formation. Strontium ranelate, however, appears to dissociate bone remodelling by simultaneously increasing bone formation and decreasing bone resorption (see Figure 1).

In animal models, strontium ranelate has been shown to increase bone formation by stimulating preosteoblast replication, resulting in an increase in bone matrix synthesis by mature osteoblasts. Additionally, it decreases bone resorption by inhibiting osteoclast activity and differentiation.³ This dual action on bone metabolism, although incompletely understood, rebalances bone turnover in favour of bone formation. Data on bone marker changes, although modest compared to other drugs,⁴ support a likely dual action.

Phase III clinical studies in postmenopausal women showed that levels of serum bone-specific alkaline phosphatase – an index of bone formation – were significantly

increased after three years' treatment with strontium ranelate.¹ Similarly, it was shown that the urinary excretion of NTX pyridinoline (type I collagen cross-linked N-telopeptide pyridinoline), a marker of bone resorption, was significantly reduced over a three-year period.¹

Efficacy against vertebral fractures

Clinical studies have shown that treatment of postmenopausal osteoporosis with strontium ranelate results in early and sustained reductions in the risk of vertebral fractures, whether or not women have already had a fracture.

The randomised Spinal Osteoporosis Therapeutic Intervention (SOTI) trial of strontium ranelate (2g per day) in 1649 postmenopausal women with established osteoporosis (low BMD) and a history of fractures showed a 49 per cent risk reduction in the incidence of new vertebral fractures in the first year of treatment, and 41 per cent overall during the three-

year study period (relative risk 0.59; 95% CI 0.48 to 0.73). The number of women needed to treat (NNT) with strontium ranelate to prevent one fracture was only nine, which compares favourably with other drugs.¹

Strontium ranelate also reduced the incidence of new symptomatic vertebral fractures by 52 per cent as early as the first year of treatment, with this benefit continuing.¹ In addition, it increased BMD by 14.4 per cent at the lumbar spine after three years, and 8.1 per cent at the femoral neck ($p < 0.001$ for both, see Figure 2). Caution is needed in interpretation of these results as up to 50 per cent of BMD changes may be artefactual, although the increased size of the BMD change with strontium ranelate may be helpful in allowing earlier assessment of treatment compliance.⁴

The Treatment Of Peripheral Osteoporosis (TROPOS) study demonstrated the value of strontium ranelate in reducing vertebral fractures in postmenopausal women with or without a history of vertebral fracture.² In the five-year study, 5091 women were randomised to strontium ranelate (2 per day) or placebo with a main statistical analysis over three years of treatment.

In 3640 women with spinal fractures, there was an overall reduction in vertebral fractures of 39 per cent. In a subgroup of 2416 women without vertebral fractures at the start of the study, the risk of subsequent vertebral fracture was reduced by 45 per cent.²

Efficacy against non-vertebral fractures

The TROPOS study also confirmed the beneficial effects of treatment on all nonvertebral fractures and in a high-risk subgroup – on hip fractures.²

After three years' treatment, there was a 16 per cent reduction in the risk of nonvertebral fractures ($p=0.04$) in strontium ranelate-treated patients, and a 19 per cent reduction in major fragility fractures such as those of the hip, wrist, pelvis and sacrum, ribs and sternum, clavicle and humerus ($p=0.031$).

In the large high-risk subgroup (selected by the European Medicines Agency) of 1977 elderly osteoporotic women aged 74 and over with low BMD (T-score ≤ -3), hip fracture risk was reduced by 36 per cent ($p<0.046$).

Strontium ranelate increased BMD throughout the study; at the three-year analysis, there was an 8.2 per cent increase at the femoral neck and a 9.8 per cent increase in the total hip.²

Pooled data from the SOTI and TROPOS studies on 1488 women aged 80 and over have demonstrated the efficacy of strontium ranelate in the very elderly.⁵ Over three years, risk of vertebral fracture was reduced by 32 per cent and of nonvertebral fracture by 31 per cent.

Effects on quality of life

Strontium ranelate is one of the few antiosteoporotic drugs with data to demonstrate an improvement in quality of life indices. Standardised questionnaires given to 1240 patients taking part in clinical trials demonstrated an improvement in global quality of life in patients treated with the drug, compared to deterioration in the placebo group ($p=0.03$). Similar differences in favour of strontium ranelate were seen in both emotional ($p=0.04$) and physical ($p=0.05$) scores.⁶

Safety and tolerability

The overall rate of adverse events in the recent randomised trials of

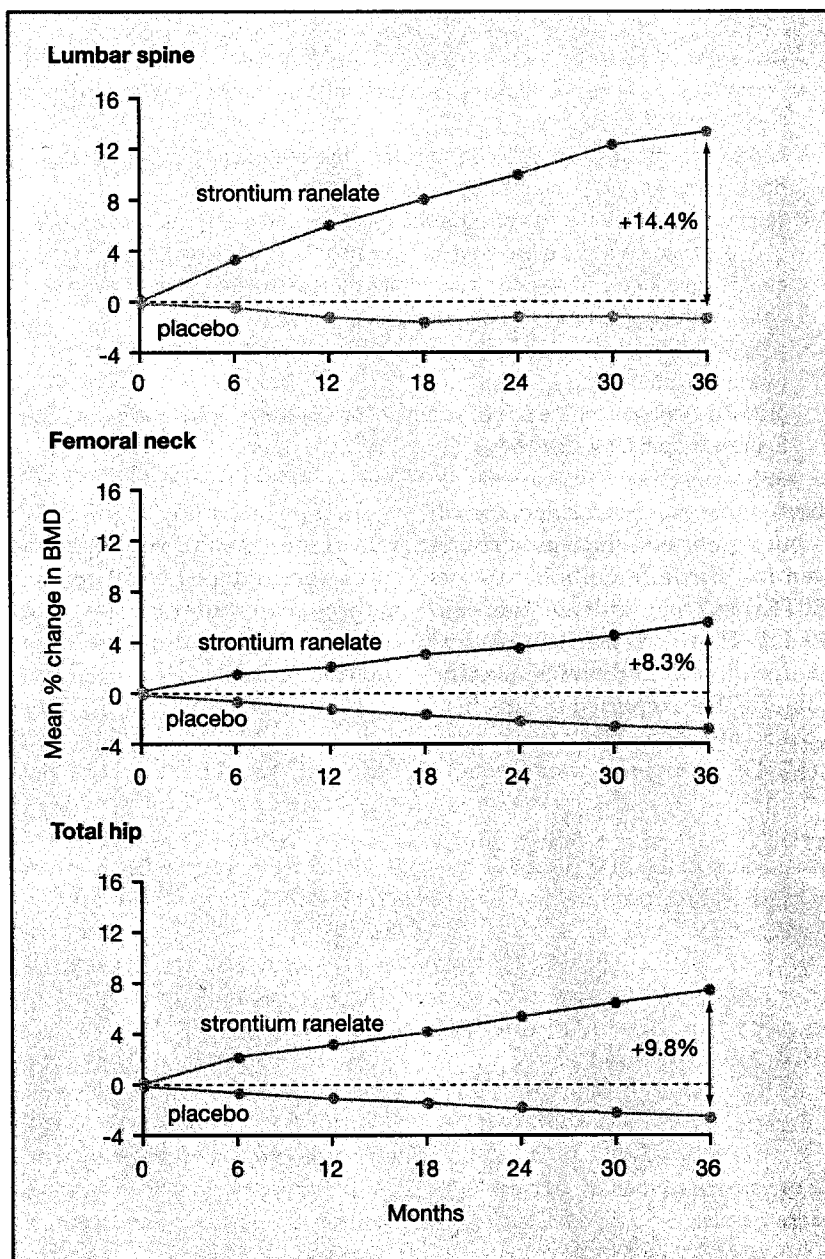


Figure 2. Effects of strontium ranelate (2g per day) on BMD in postmenopausal women with established osteoporosis and a history of fractures ($p<0.001$ for all comparisons)

strontium ranelate was similar to that in the placebo group, as found in previous studies.^{1,2} This translated into good compliance, with a compliance rate of 83 per cent in women treated with the active drug compared to 85 per cent in the placebo group.

Diarrhoea was the most common GI adverse event seen in clinical trials. In SOTI, diarrhoea

affected 6.1 per cent of patients in the strontium ranelate group compared with 3.6 per cent taking placebo.¹ In TROPOS, the figures were 6.7 per cent vs 5 per cent respectively.² In both trials, this side-effect resolved after the first three months of treatment.

No increases in upper GI symptoms compared to placebo were observed.^{1,2} When a meta-analysis of

Key points

- strontium ranelate is the first in a new class of osteoporosis therapies called Dual Action Bone Agents
- has a novel mode of action: it dissociates bone remodelling by increasing bone formation while decreasing bone resorption
- licensed to reduce the risk of vertebral fractures and is the first nonbisphosphonate treatment to be licensed for the reduction of hip fractures
- comparable in tolerability, efficacy, safety and ease of use to bisphosphonates, without the upper GI concerns
- a 2g powder that should be taken once daily at bedtime, preferably at least two hours after eating
- growing evidence for the use of strontium ranelate as an alternative first-line treatment option for osteoporosis

both studies was performed, a small – but significant – increased risk of venous thromboembolic events (VTEs) was seen with an odds ratio of 1.4. There was no clear clinical pattern to this and no haemostatic abnormalities reported to explain it, so it is unclear whether this is a statistical quirk or a real phenomenon. In any case, the risk is small compared to HRT or oral contraceptive usage and on the SPC there is a caution – not a contraindication – until further data are available.

Strontium can interfere with precise blood calcium measurements if routine techniques are used, but specialised assays can be employed if a clinically relevant false-high reading is obtained.

Comparison with other products

The 40-50 per cent reduction in the risk of vertebral fractures, and the 36 per cent reduction in hip fracture rate in a high-risk population, are similar to those seen with other osteoporosis treatments, although each study has different populations.

For example, in bisphosphonate trials, reductions of 37-57 per cent have been reported in vertebral fractures, with reductions of 34-51 per cent in hip fractures, although many estimates are based on small numbers.⁷

In a pivotal study of the SERM raloxifene (Evista), vertebral fractures were reduced by 30 per cent at three years, but there was no significant effect on nonvertebral or hip fractures.⁸

Parathyroid hormone (teriparatide) has been shown to reduce vertebral fractures by 65 per cent and nonvertebral fractures by 53 per cent over a median 21 months in women with previous vertebral fractures, although numbers were small.⁹ Teriparatide has not yet demonstrated efficacy on hip fracture and is given as a costly daily injection.

In terms of overall efficacy, safety, tolerability and ease of use, strontium ranelate is comparable with the most widely used treatment for osteoporosis – bisphosphonates – without the upper GI concerns.

Where does strontium ranelate fit in?

Used alongside daily calcium and vitamin D, strontium ranelate offers physicians another useful treatment option for a condition that is associated with significant morbidity and mortality and carries a high social and economic burden.⁷

In its recent guidance on the use of bisphosphonates, raloxifene and teriparatide, the

National Institute for Health and Clinical Excellence (NICE) drew attention to the importance of identifying and treating women who have already had an osteoporotic fragility fracture.⁷ A further technology assessment on the role of strontium ranelate is already underway and this, together with additional guidance on primary prevention of osteoporosis, is expected to be published early in 2006.

Good compliance is essential for the long-term treatment of osteoporosis and prevention of fractures and, to this end, all advances in therapy that increase the choice of effective treatment available to physicians and their patients are to be welcomed. Most women are already using a once-weekly formulation of bisphosphonate, and the introduction of a once-a-month oral formulation of ibandronate (Bonviva) adds further to the range of treatments on offer. Some will prefer these infrequent dosage regimens and others the regular night-time strontium ranelate drink, depending on factors such as age, memory, meal habits and concomitant therapy.

Conclusion

Strontium ranelate offers promising protection against vertebral and nonvertebral osteoporotic fractures. Its efficacy has been demonstrated in all postmenopausal age groups, including the very elderly, for whom few drugs have comparable data.

Strontium ranelate is well tolerated and easy to use with a novel action different to the bisphosphonates. Growing evidence supports the use of strontium ranelate as an additional option in the first-line management of the disease, especially for those intolerant of – or with concomitant – conditions such as dyspepsia or heartburn,

that may preclude the use of bisphosphonates.

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Declaration

Professor Spector is a consultant to Servier as well as other pharmaceutical companies.

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