

# NEW DRUG EVALUATION

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## STRONTIUM RANELATE

Strontium ranelate is licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. It has a novel mode of action, both increasing bone formation and reducing bone resorption. It reduces the risk of vertebral and non-vertebral fractures compared with placebo but has not been directly compared with other osteoporosis treatments. Adverse effects include nausea and diarrhoea. Strontium ranelate is an alternative choice of therapy for postmenopausal osteoporosis, particularly for those unable to comply fully with bisphosphonate dosing instructions.

### What is it?

Strontium ranelate (Protelos<sup>®</sup>, Servier Laboratories) is licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. It has a novel mode of action, both increasing bone formation and reducing bone resorption.<sup>1</sup> One 2g oral sachet should be taken daily in a glass of water, at bedtime, at least 2 hours after eating as its absorption is reduced by food, milk and other calcium-containing products.<sup>1</sup> Patients should also receive calcium and vitamin D supplements if their dietary intake is inadequate.<sup>1</sup> It is currently only licensed for use in postmenopausal women; its efficacy and safety have not been demonstrated in other patient groups. No dosage adjustment is required in the elderly.<sup>1</sup>

### How effective is it?

The efficacy of strontium ranelate in the treatment of postmenopausal osteoporosis is based on 36-month data from two ongoing prospective 5-year phase III RCTs.<sup>2,5</sup> Both trials were conducted in Caucasian women aged >50yrs also receiving calcium and vitamin D supplements. The first trial focused on vertebral fractures<sup>2</sup> and the second primarily on non-vertebral fractures.<sup>3,4</sup>

The World Health Organisation classification of osteoporosis is based on the measurement of bone mineral density (BMD), with reference to the number of standard deviations from the BMD in an average 25-year-old woman (T-score). A T-score of >-1 is considered normal, -1 to -2.5 indicates osteopaenia, <-2.5 indicates osteoporosis and <-2.5 plus at least one fragility fracture indicates established osteoporosis.<sup>6</sup>

In the first study, 1,649 postmenopausal women (mean 69.7yrs) with at least one prevalent vertebral fracture plus a lumbar-spine BMD of  $\leq 0.84\text{g/cm}^2$  (87.5% with lumbar BMD T-score <-2.5) received either 2g/day strontium ranelate or placebo.<sup>2,5</sup> The primary outcome (restricted to patients with both baseline and after-baseline radiographs (n=1,442)) was the incidence of new vertebral fractures.<sup>2,5</sup> At 36 months, the incidences of new vertebral fractures confirmed by radiological imaging with strontium ranelate and placebo were 20.9% and 32.8%, respectively (absolute risk reduction (ARR) 11.9%;  $p < 0.001$ ).<sup>2,5</sup> This implies that 9 patients need to be treated for 3 years to prevent one patient experiencing a new vertebral fracture.

In the second study, 5,091 postmenopausal osteoporotic women aged  $\geq 74$ yrs or between 70-74yrs with one additional risk factor (frequent falls; personal or maternal history of postmenopausal osteoporotic fracture; retirement home resident) and a femoral neck BMD T-score <-2.5 were randomised to strontium ranelate 2g/day or placebo.<sup>4</sup> The primary endpoint (incidence of osteoporotic non-vertebral fracture, restricted to patients with documented non-vertebral fracture (n=4,932)) was seen in 9.4% of patients on strontium ranelate compared with 11.2% on placebo over 36 months (ARR 1.85%;  $p = 0.04$ ).<sup>4</sup> This implies that 55 patients need to be treated for 3 years to prevent one patient experiencing a non-vertebral fracture.

This trial did not show a significant difference between strontium ranelate and placebo for proximal femur fracture ( $p = 0.33$ ), the key peripheral fracture site for a therapeutic claim.<sup>5</sup> To address this, a *post hoc* analysis was conducted in a subset of 1,977 women aged  $\geq 74$ yrs (mean 80yrs) with established osteoporosis (baseline femoral neck BMD T-score  $\leq -3.0$ ; mean T-score -3.6).<sup>4</sup> Over 36 months, the analysis showed borderline efficacy in reduction of hip fracture with strontium ranelate (4.3%) compared with placebo (6.4%; ARR 2.1%;  $p = 0.046$ ; number needed to treat (NNT) 48).<sup>4</sup> This type of analysis has previously been used in approving therapeutic indications for other bisphosphonates.<sup>5</sup>

### How safe is it?

Overall, adverse event incidence rates with strontium ranelate did not differ from placebo and were usually mild and transient.<sup>1</sup> The most common were nausea and diarrhoea. Phase III clinical trials showed that, compared with placebo, strontium ranelate was associated with an increased annual incidence of venous thromboembolism (VTE) of 0.7% (RR 1.42;  $p = 0.036$ ); however, the mechanism is unknown.<sup>1</sup> Strontium ranelate should be used with caution in patients at increased risk of, VTE.<sup>1</sup>

### What other options are there?

Drug Update No. 28 reviewed options for the prevention of postmenopausal osteoporosis.<sup>8</sup> Technology Appraisal No. 87 issued by NICE<sup>6</sup> recommends bisphosphonates (alendronate, risedronate and etidronate)

as treatment options for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. All women should have normal calcium and/or vitamin D intake either via diet or supplementation.

Raloxifene is recommended as an alternative in the above group if bisphosphonates are contra-indicated or not tolerated or if patients are unable to comply with recommendations for use or have an unsatisfactory response. Teriparatide is recommended for those  $\geq 65$  yrs who have an unsatisfactory response to or are intolerant of bisphosphonates.

NICE Technology appraisals for the primary prevention of osteoporotic fractures in postmenopausal women and strontium ranelate for the treatment of osteoporosis are expected in September 2005 and March 2006, respectively.

A NICE osteoporosis guideline on the assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk is expected in Feb 2006.

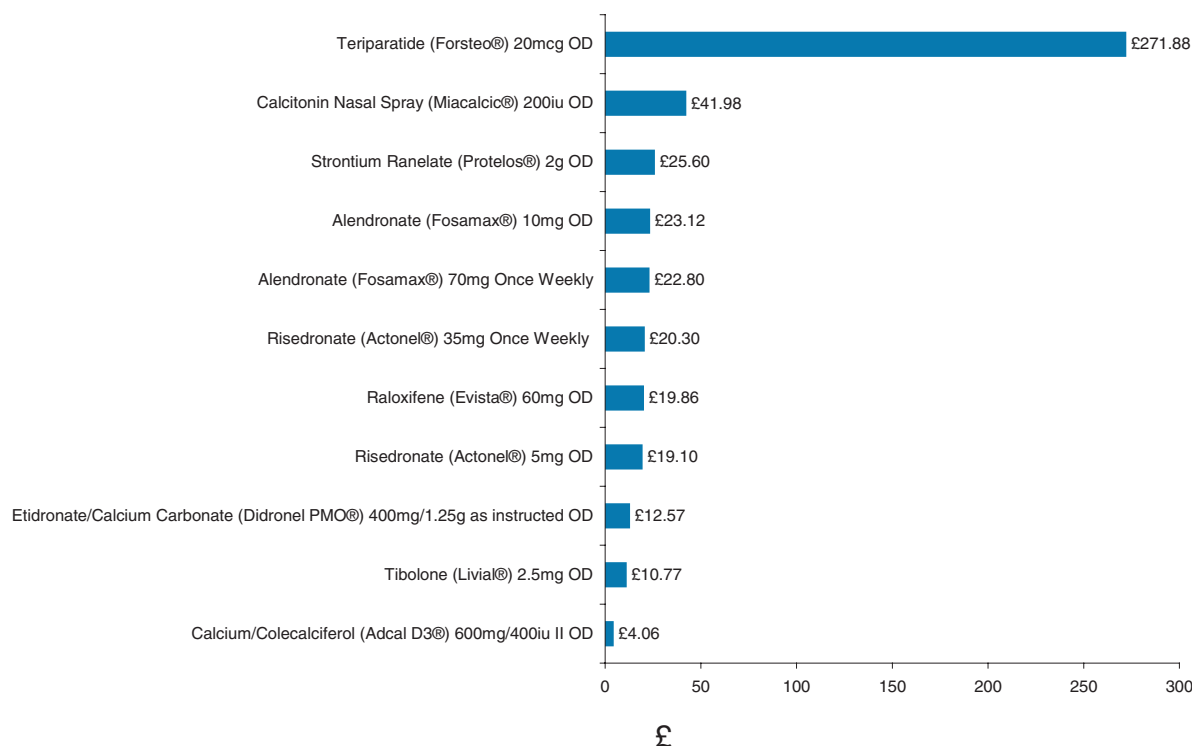
### When should it be used?

Strontium ranelate is licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures, not for the prevention of postmenopausal osteoporosis.

Established therapies such as alendronate, risedronate and etidronate remain first-line treatments for confirmed postmenopausal osteoporosis.<sup>6</sup> Strontium ranelate is an alternative for the treatment of postmenopausal osteoporosis, particularly for those unable to comply fully.

### How much does it cost?

#### Cost of 28 Days Treatment (MIMS/Drug Tariff April 2005)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT-randomised controlled trial, G-guideline, R-review, U-unpublished, Abs- abstract,

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