

# **The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women**

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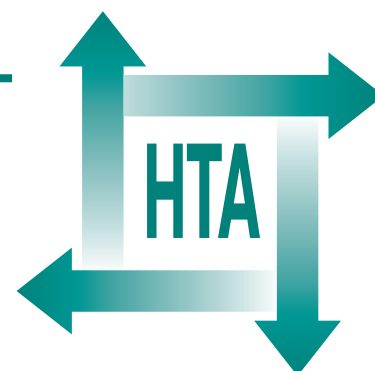
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## ***Executive summary***

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## Executive summary

### Objectives

The review aims to estimate the clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fractures in postmenopausal women, at different levels of absolute fracture risk. This considers secondary prevention in women who have sustained a previous fracture and primary prevention in those women without a previous fracture, as women with osteoporosis are asymptomatic until a fracture is sustained.

### Epidemiology and background

Osteoporosis is a common disease in the elderly, with an estimated 1.1 million female sufferers in England and Wales. It is defined as possessing a *T*-score of  $-2.5$  standard deviations or lower. The main consequence of osteoporosis is an increased incidence of fractures, which increase as a woman ages. These result not only in morbidity for the patient (with a risk of mortality following fractures at some sites), but also in the consumption of scarce NHS resources. A recent estimate of the projected cost in the UK by 2010 of osteoporotic fractures in females put this figure at £2.1 billion.

### Methods

A systematic review was carried out to determine clinical effectiveness. Major electronic bibliographic databases were searched in September 2004 and updated in March 2005. In addition, the reference lists of relevant articles and sponsor submissions were handsearched. Data from selected studies were assessed and included in the meta-analyses, if appropriate.

The model used to calculate cost-effectiveness ratios was an updated version of Sheffield Health Economic Model for Osteoporosis. The model calculated the number of fractures that occur and provided as output data the costs associated with osteoporotic fractures, and the quality-adjusted life-years (QALYs) accrued by a cohort of 100

osteoporotic women, with each fracture being detrimental to health and incurring a cost. When the costs of the intervention were included, the incremental cost compared with no treatment was calculated and divided by the gain in QALYs to calculate cost-effectiveness measures. Treatment with strontium ranelate was calculated against a no-treatment option to evaluate whether it could be given cost-effectively. An incremental analysis against alendronate was also conducted to estimate the cost-effectiveness of strontium ranelate relative to a current standard treatment. The cost-effectiveness of strategies for identifying and treating women without a prior fracture used the risk of fracture as an input to the cost-effectiveness model.

### Results

#### Number and quality of studies, and direction of evidence

Three trials (the STRATOS, SOTI and TROPOS studies) were identified which compared strontium ranelate with placebo in postmenopausal women with osteoporosis and reported fracture outcomes. Participants also received calcium and vitamin D supplements, with the exception of participants in SOTI and TROPOS, whose daily dietary calcium intake exceeded 1000 mg; these women only received vitamin D supplements.

Pooled data from SOTI and TROPOS indicate that strontium ranelate therapy is associated with a significant reduction in the risk of vertebral fracture [relative risk (RR) compared with placebo 0.60, 95% confidence intervals (CI) 0.53 to 0.69,  $p < 0.001$ ] and non-vertebral fracture (RR 0.84, 95% CI 0.73 to 0.97,  $p = 0.01$ ). The studies were not powered to identify a statistically significant difference in the incidence of fracture at any specific peripheral fracture site.

#### Safety

In general, strontium ranelate therapy did not seem to be associated with an increased risk of adverse events. Most adverse events were mild and transient. However, the risk of one rare but serious adverse event, venous

thromboembolism (including pulmonary embolism), was found to be significantly higher in patients receiving strontium ranelate compared with placebo (RR 1.42, 95% CI 1.02 to 1.98,  $p = 0.036$ ). Some nervous system disorders, including mental impairment, disturbed consciousness, memory loss and seizures, were also more common in patients randomised to strontium ranelate. Both of these issues are being addressed in the ongoing extension of the SOTI and TROPOS studies and by postmarketing surveillance.

### Summary of benefits

Benefits were measured in terms of QALYs. Strontium ranelate provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the absolute risk of fracture.

### Cost-effectiveness of identification and treatment strategies

The report used a modified version of a soon-to-be published algorithm that estimates absolute fracture risk from patient characteristics. Risk factors used within the algorithm were age, gender, bone mineral density (BMD), prior fracture history, parental history of hip fracture, smoking status, alcohol consumption, rheumatoid arthritis and corticosteroid use. The results show that strontium ranelate can be used cost-effectively in women at relatively high risk of osteoporotic fracture. However, the results of the probabilistic sensitivity analysis, using efficacy data from randomised controlled trials, suggest that it is not as cost-effective as alendronate, a comparator intervention from the bisphosphonate class.

The use of strontium ranelate in women without a prior fracture will be dependent on any identification algorithms that are implemented. Such algorithms are being produced in conjunction with the National Institute for Health and Clinical Excellence Osteoporosis Guidelines Development Group (NICEGDG), and a preliminary version is reproduced in this report. It is likely that any identification strategy aimed at reducing the incidence of osteoporotic fractures will use bisphosphonates as the first line therapy. Given this, the use of strontium ranelate in such patients is likely to be low.

### Costs

Since, on the basis of the probabilistic sensitivity analyses, strontium ranelate is not expected to be the first line therapy, the introduction of this

intervention is unlikely to change significantly the overall costs associated with current osteoporosis treatments such as bisphosphonates. The acquisition cost of strontium ranelate is greater than that for bisphosphonates, and where the intervention is prescribed the cost of purchasing drugs will increase.

## Conclusions

Strontium ranelate was shown to be clinically effective in the prevention of osteoporotic fractures. Scenarios have been found where strontium ranelate can be used cost-effectively; however, given the probabilistic sensitivity analyses conducted, this intervention appears to be less cost-effective than the bisphosphonate alendronate.

Work has been presented on the cost-effectiveness of identifying asymptomatic women who could be treated cost-effectively. This work is part of an ongoing project undertaken with the NICEGDG and will be further reviewed and be used as part of the guidelines issued for the management of women at high risk of osteoporotic fracture.

## Recommendations for research

The evidence base for the efficacy of fracture prevention for strontium ranelate needs to be strengthened, particularly for hip fractures, where there is currently a non-significant reduction.

If it were believed that the efficacy of strontium ranelate is dependent on either age or absolute risk, this would need to be proven.

The evidence base on the *T*-score by age of the general female population needs to be strengthened, particularly in women over the age of 80 years. The prevalence of risk factors associated with fracture rates, over and above that provided by BMD, also needs to be significantly strengthened to ensure that the estimated number of women that could be cost-effectively treated is accurate.

Until head-to-head comparisons of strontium ranelate and bisphosphonates are undertaken, decision-makers will have to make choices based on indirect evidence; for example, comparing the results for bisphosphonates plus calcium and vitamin D versus calcium and vitamin D, with

those for strontium ranelate plus calcium and vitamin D versus calcium and vitamin D. Given the large number of patients that would be needed to show statistical difference in efficacy between patients these trials are unlikely to be conducted; however, high-quality observational databases may provide further insight into relative efficacies.

## Publication

Stevenson M, Davis S, Lloyd-Jones M, Beverley C. The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. *Health Technol Assess* 2007;**11**(4).

# NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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