

# Strontium ranelate (Protos) for postmenopausal osteoporosis

(STRON-tee-um RAN-ell-ate)

## Summary

- Strontium ranelate appears to have comparable efficacy to that of alendronate in reducing the risk of vertebral fracture in postmenopausal women with a previous fracture.
- There is some evidence that strontium reduces the risk of non-vertebral fracture — in a mixed population of postmenopausal women with and without a previous fracture — compared with placebo. However, data on hip fracture are limited.
- Strontium is only subsidised on the PBS as monotherapy in postmenopausal women.
- Use calcium and vitamin D supplementation if needed. Reduce overall fracture risk by using other additional interventions.
- Use caution if considering strontium in women at increased risk of thromboembolism.
- Oral absorption of strontium is reduced by food, calcium-containing products and antacids — take strontium at bedtime, at least 2 hours after food, calcium or antacids.

## PBS listing

### Authority required (streamlined)

On 1 November 2007 the listing of strontium ranelate was extended to the treatment of osteoporosis in some postmenopausal women without fracture (i.e. primary prevention).

Strontium was first listed on the Pharmaceutical Benefits Scheme (PBS) on 1 April 2007 for the treatment of established osteoporosis in postmenopausal women with fracture due to minimal trauma (i.e. secondary prevention).

### Primary prevention

Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a woman aged  $\geq 70$  years with a bone mineral density (BMD) T-score  $\leq -3.0$ .<sup>1</sup> The date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the woman's medical record when treatment is initiated.

### Secondary prevention

Treatment as the sole PBS-subsidised anti-resorptive agent for established postmenopausal osteoporosis in a woman with fracture due to minimal trauma.<sup>2,3</sup> The fracture must have been demonstrated radiologically and the year of plain X-ray, computed tomography (CT) scan or magnetic resonance imaging (MRI) must be documented in the woman's medical record when treatment is initiated.

### Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended strontium ranelate for listing on a cost-minimisation basis — that is, similar efficacy and cost compared with alendronate — for reducing the risk of fracture in postmenopausal women aged  $\geq 70$  years with a BMD T-score  $\leq -3.0$  (i.e. primary prevention); and for the outcome of morphometric vertebral fracture\* in established postmenopausal osteoporosis (i.e. secondary prevention).<sup>1,3,4</sup>

\* A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid-portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared with the vertebral body above or below the affected vertebral body.

The PBAC recommended that strontium should not be PBS subsidised for concomitant use with other PBS-listed anti-resorptive drugs. The PBAC recognised that, given the different mechanism of action of other PBS-listed anti-resorptives, there was a potential for strontium to be added to current therapy. Thus the PBAC recommended that the restricted listing for strontium — as for all PBS-listed anti-resorptives — preclude PBS subsidisation of concomitant therapy with other PBS-listed anti-resorptives.<sup>3,4</sup> At present there is no evidence to suggest that combining anti-resorptive therapy results in greater reduction of fracture incidence, although there may be an increased risk of adverse effects.

## Place in therapy

Strontium ranelate reduces the risk of vertebral fracture in women with a previous fracture. There is some evidence that strontium reduces non-vertebral fracture in a mixed population of women with and without a previous fracture. Evidence for strontium reducing hip fracture risk is less robust because it is limited to a post-hoc analysis of a high-risk subgroup of these women.

Clinical trials and meta-analyses show that the bisphosphonates alendronate and risedronate reduce the risk of vertebral, non-vertebral and hip fracture.

Alendronate, risedronate or strontium may be used as initial therapy for postmenopausal osteoporosis. However, strontium has limited data for an effect on hip fractures; there is less experience of its use and its long-term safety profile is less established. Some unpublished 5-year efficacy data are available for strontium.<sup>5</sup> There are published data for up to 7 years with risedronate,<sup>6</sup> and up to 10 years with alendronate.<sup>7,8</sup> Consider using strontium for women:

- who cannot tolerate bisphosphonates (e.g. because of gastrointestinal adverse effects, including oesophageal ulceration)
- who are unable to administer bisphosphonates correctly (e.g. needing to sit upright after administration)
- for whom bisphosphonates are contraindicated (e.g. oesophageal abnormalities that delay oesophageal emptying, such as stricture or achalasia).

Refer to *NPS News 53: Maintaining bone health to prevent osteoporotic fractures*<sup>9</sup> and *Prescribing Practice Review 39: Preventing osteoporosis and reducing fracture risk*<sup>10</sup> for more information about other therapies for osteoporosis.

Strontium reduces bone resorption and increases bone formation — an additional mechanism to that of bisphosphonates (which only reduce bone resorption) and an alternative mechanism to that of raloxifene (a selective oestrogen-receptor modulator).<sup>11,12</sup>

Adverse effects of strontium are generally mild and transient (see Safety issues).

Strontium is distributed in bone and increases X-ray absorption compared with calcium. This amplifies bone density measurements by dual energy X-ray absorptiometry (DEXA) and may account for about 50% of measured changes.<sup>11,13</sup> Women taking strontium should be identified as such when undergoing a DEXA scan so that this can be taken into account when interpreting the results.

Strontium ranelate is a new form of oral strontium and should not be confused with the radioactive isotope, strontium-89, which is used to treat metastatic bone pain.<sup>12</sup>

## Strontium is approved for use in postmenopausal women only


The average age of women enrolled in the two key trials of strontium was about 70 years and 77 years; they had been postmenopausal for more than 20 years.<sup>13,14</sup>

There is currently no evidence for the use of strontium in premenopausal women, men with osteoporosis or corticosteroid-induced osteoporosis.

## Strontium has not been directly compared with other drugs used in osteoporosis

Two placebo-controlled trials have investigated the effect of strontium on vertebral and non-vertebral fractures: the Spinal Osteoporosis Therapeutic Intervention (SOTI) study and the Treatment of Peripheral Osteoporosis (TROPOS) study.<sup>13,14</sup>


There are no direct head-to-head comparisons between strontium and other drugs used for osteoporosis. Indirect comparisons with alendronate (using placebo as the common comparator) were used in both submissions to the PBAC.<sup>1,3</sup> For primary prevention the results for strontium in the TROPOS trial were compared against those of alendronate in the Fracture Intervention Trial (FIT-2)<sup>15</sup>; and for secondary prevention, the results for strontium in the SOTI trial were compared against those of alendronate in the Fracture Intervention Trial (FIT-1).<sup>16</sup>

These indirect comparisons suggest that both strontium and alendronate may reduce fracture risk to a similar extent; however, important differences in the trial populations make it difficult to compare the efficacy of these drugs. [www](#) 

### Strontium appears to have a similar magnitude of effect to that of alendronate for vertebral fracture

Strontium reduced the risk of new vertebral fracture in placebo-controlled trials. In a subgroup of women without a previous fracture (i.e. primary prevention) enrolled in TROPOS, strontium reduced the risk of new vertebral fracture by 45% (relative risk [RR] 0.55, 95% confidence interval [CI] 0.42 to 0.72,  $p = 0.001$ ). However, TROPOS was not designed to detect a difference in new vertebral fracture for this group.<sup>13</sup>

For women with previous fracture (i.e. secondary prevention), the relative risk estimates for new vertebral fracture were similar for strontium and alendronate when compared with placebo after 3 years of treatment (see Table 1).

[www](#)  Refer to this review at [www.nps.org.au](http://www.nps.org.au) for additional information on differences between trial populations used for indirect comparisons between strontium and alendronate.

**Table 1: Number of women with new morphometric vertebral fracture after 3 years<sup>3</sup>**

Study	Strontium	Placebo	Alendronate	Relative risk <sup>a</sup> (95% CI)
SOTI (strontium)	150/719 (20.9%)	237/723 (32.8%)		0.59 (0.48 to 0.73)
FIT-1 (alendronate)		145/965 (15.0%)	78/981 (8.0%)	0.53 (0.41 to 0.68)

<sup>a</sup> Indirect comparison estimate of relative risk: RR 1.1, 95% CI 0.8 to 1.6

CI = confidence interval; SOTI = Spinal Osteoporosis Therapeutic Intervention study<sup>14</sup>; FIT-1 = Fracture Intervention Trial<sup>16</sup>

**Table 2: Number of women with clinical vertebral fracture after 3 years**

Study	Strontium	Placebo	Alendronate	Relative risk <sup>c</sup> (95% CI)
SOTI <sup>b</sup> (strontium)	11.3%	17.4%		0.62 (0.48 to 0.83)
FIT-1 (alendronate)		50/965 (5.0%)	23/981 (2.3%)	0.45 (0.27 to 0.72)

<sup>b</sup> Total number of patients with symptomatic vertebral fracture after 3 years = 192; the number of patients for each of the strontium and placebo groups was not reported

<sup>c</sup> Indirect comparison estimate of relative risk RR 1.4, 95% CI 0.8 to 2.5

CI = confidence interval; SOTI = Spinal Osteoporosis Therapeutic Intervention study<sup>14</sup>; FIT-1 = Fracture Intervention Trial<sup>16</sup>

Both trials reported clinical fractures: in SOTI these were defined as acute back pain, a decrease in body height of at least 1 cm, or both; in FIT-1 clinical fractures were reported by study participants and confirmed radiologically. The effect on the incidence of clinical vertebral fracture is shown in Table 2.

### **There is some evidence that strontium reduces the risk of non-vertebral fracture compared with placebo**

The TROPOS study had non-vertebral fractures as the primary outcome in a mixed population of women with and without a previous fracture.<sup>13</sup> Treatment with strontium showed a 16% relative risk reduction in the incidence of non-vertebral fractures compared with placebo after 3 years (RR 0.84, 95% CI 0.70 to 1.00,  $p = 0.04$ ). In women enrolled in the SOTI study, strontium had no effect on the risk of non-vertebral fracture (RR 0.90, 95% CI 0.69 to 1.17). However, the SOTI study was not powered for this outcome.<sup>14</sup>

### **Evidence that strontium reduces hip fracture risk is limited to a post-hoc analysis of a high-risk subgroup**

Strontium did not reduce hip fracture risk in the total TROPOS population (an outcome for which the study was not designed or powered). Reduced hip fracture risk was shown in a post-hoc subgroup analysis of 1977 women (39% of the TROPOS population, 58% of whom had a previous fracture) aged  $\geq 74$  years with femoral neck BMD T-score  $\leq -3.0$  (RR 0.64, 95% CI 0.41 to 1.00,  $p < 0.046$ ).<sup>13</sup> However, differences found in post-hoc subgroup analyses are more likely to be due to chance. The evidence that strontium reduces hip fracture risk is therefore limited and requires confirmation. Strontium has not been shown to reduce hip fracture risk in a primary prevention population.

In contrast, alendronate significantly reduced hip fracture risk in FIT-1 (secondary outcome) in women with established osteoporosis.<sup>16</sup> In FIT-2 (where hip fracture was part of the primary outcome of any clinical fracture) alendronate reduced hip fracture risk in a subgroup of women without vertebral fractures at baseline who had a femoral neck BMD T-score  $< -2.5$ . According to the published FIT-2 paper, this was a pre-planned subgroup analysis before unblinding of the trial.<sup>15</sup> Risedronate significantly reduced the risk of hip fracture (a primary outcome) in women with osteoporosis aged 70–79 years (38% of whom had vertebral fractures at baseline).<sup>17</sup>

### **Ensure adequate intake of calcium and vitamin D to help prevent fractures**

Adequate calcium intake and optimal vitamin D levels are important when managing osteoporosis.<sup>18</sup> As with other trials of anti-resorptive drugs, all women in strontium trials who had low calcium and vitamin D levels received supplements. Ensure an adequate daily intake, which for women aged over 70 years is 1300 mg calcium and 600 units vitamin D.<sup>19,20</sup> Use a calcium supplement if dietary calcium intake is inadequate, and correct vitamin D deficiency if present.

Calcium-containing products must be separated by at least 2 hours from the strontium dose (see Dosing issues).

### **Other interventions remain important for modifying fracture risk**

Many risk factors are at least partly independent of BMD and may not be modified by drug therapy (see Box 1). Use other interventions to maintain BMD or help reduce fracture risk, such as smoking cessation, reduced alcohol intake, weight bearing and resistance exercise (depending on age), balance training, hip protectors and occupational therapy.<sup>21,22</sup>

### **Safety issues**

The most frequent adverse effects associated with strontium ranelate are nausea, diarrhoea, headache, dermatitis and eczema.<sup>25</sup> Nausea and diarrhoea were generally reported at the beginning of treatment, with no difference between strontium and placebo groups after 3 months.<sup>13,14</sup>

Use strontium with caution in women considered at risk or with a history of thromboembolic disorders. If prescribing strontium for these women, regularly monitor for possible signs of venous thromboembolism (such as leg swelling, redness or pain that may worsen when walking or standing and/or shortness of breath or chest pain that may worsen with deep breaths). Treatment with strontium has been associated with an increased annual incidence of venous thromboembolism (0.9%) (including pulmonary embolism), relative to placebo (0.6%).<sup>25,26</sup> Four-year data from ongoing clinical trials showed the increased risk remained similar.<sup>27</sup>

**Box 1: Risk factors for osteoporotic fracture<sup>23,24</sup>**

Independent of BMD*	Dependent on BMD
Advanced age	Female gender
Previous fragility fracture	Asian or Caucasian race
Glucocorticoid use	Menopause
Family history of fragility fracture	Prolonged amenorrhoea
Falls†	Hypogonadism in men
High bone turnover	Low dietary calcium
Low body weight	Prolonged immobilisation
Cigarette smoking	Vitamin D deficiency
Excessive alcohol intake	

\* Independent factors contribute to fracture risk over and above that of low BMD

† The risk of falls increases with age, previous falls, poor visual acuity, cognitive impairment, problems with gait and balance, reduced mobility and sedative use.

CNS effects (including disturbed concentration, memory loss and seizures) are rare (incidence < 0.1%)<sup>11</sup> although more frequent in people over 80 years or with a creatinine clearance < 30 mL/min.<sup>27</sup>

Serum calcium concentrations decreased and phosphate concentrations increased in trials but were not associated with any clinical consequences.<sup>27</sup>

Transient reversible increases in creatine kinase concentrations have been reported but were not associated with any increase in clinical muscular symptoms.<sup>14</sup>

Strontium has been available in Germany and the UK since October 2004, and in most European countries since the end of 2005. However, as with any new drug, the full toxicity profile and long-term effects of strontium are unknown. Use strontium with caution until more experience accumulates.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see [www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

**Dosing issues**

The recommended dose of strontium is 2 g orally once daily, preferably at bedtime. The contents of the 2 g sachets must be mixed with at least 30 mL of water (about one-third of a standard glass).<sup>11,25</sup>

The oral bioavailability of strontium is reduced by calcium, oral tetracyclines and food. Therefore strontium should be taken at least 2 hours after food, milk or other dairy products, calcium-containing medicines or tetracyclines. Similarly, antacids containing aluminium or magnesium should be separated by at least 2 hours from the strontium dose.<sup>11,12,25</sup>

No dosage adjustments are required in relation to age, even in the very elderly — women up to 100 years of age were included in clinical trials.<sup>25</sup>

**Information for patients**

Highlight the importance of lifestyle in improving bone health and reducing the risk of falls and fractures. In particular, ensure adequate intake of calcium and vitamin D, either dietary or with supplementation, and encourage women to undertake a physical activity program to improve muscle strength and balance.

Advise women to take strontium at bedtime, at least 2 hours after food, calcium-containing products or antacids.

Advise women to contact their doctor if they experience signs of venous thromboembolism in the leg (swelling, redness or pain that may worsen when walking or standing) or lungs (shortness of breath or chest pain that may worsen with deep breaths).

Suggest or provide the Protos consumer medicine information (CMI) leaflet.

**Medicine Update** 

An NPS *Medicine Update* leaflet on strontium is available for consumers. *Medicine Update* helps consumers to ask the right questions about new medicines and helps them compare the potential benefits and harms of a new medicine with other medicines.

## References

1. Pharmaceutical Benefits Advisory Committee. July 2007 Positive recommendations. Canberra: Australian Government Department of Health and Ageing, 2007. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-july07-positive> (accessed 20 August 2007).
2. Department of Health and Ageing. PBS for Health Professionals. Canberra, 2007. [www.pbs.gov.au](http://www.pbs.gov.au) (accessed 30 April 2007).
3. Pharmaceutical Benefits Advisory Committee. Public summary document: strontium ranelate sachet containing granules for oral suspension, 2g. Canberra: Australian Government Department of Health and Ageing, 2005. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-strontium> (accessed 28 March 2007).
4. Pharmaceutical Benefits Advisory Committee. July 2005 Positive recommendations. Canberra: Australian Government Department of Health and Ageing, 2005. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-jul05-positive#stro> (accessed 28 March 2007).
5. Reginster JY, et al. Osteoporos Int, 2006;17 (Suppl 2):Conference abstract OC24.
6. Mellström DD, et al. Calcif Tissue Int 2004;75:462–8.
7. Black DM, et al. JAMA 2006;296:2927–38.
8. Bone HG, et al. N Engl J Med 2004;350:1189–99.
9. National Prescribing Service. Maintaining bone health to prevent osteoporotic fractures. NPS News 53. Sydney: National Prescribing Service, 2007. [http://nps.org.au/site.php?content=/html/news.php&news=/resources/NPS\\_News/news53](http://nps.org.au/site.php?content=/html/news.php&news=/resources/NPS_News/news53) (accessed 3 August 2007).
10. National Prescribing Service. Preventing osteoporosis and reducing fracture risk. Prescribing Practice Review 39. Sydney: National Prescribing Service, 2007. [http://nps.org.au/site.php?content=/html/ppr.php&ppr=/resources/Prescribing\\_Practice\\_Reviews/ppr39](http://nps.org.au/site.php?content=/html/ppr.php&ppr=/resources/Prescribing_Practice_Reviews/ppr39) (accessed 4 September 2007).
11. Australian Medicines Handbook, 2007.
12. Sweetman S, ed. Martindale: The Complete Drug Reference Updated periodically (Thomson Micromedex). London: Pharmaceutical Press, 2006.
13. Reginster JY, et al. J Clin Endocrinol Metab 2005;90:2816–22.
14. Meunier PJ, et al. N Engl J Med 2004;350:459–68.
15. Cummings SR, et al. JAMA 1998;280:2077–82.
16. Black DM, et al. Lancet 1996;348:1535–41.
17. McClung MR, et al. N Engl J Med 2001;344:333–40.
18. Reginster JY. BMJ 2005;330:859–60.
19. Osteoporosis Australia. Calcium, vitamin D and osteoporosis – a guide for GPs. Canberra: Australian Government Department of Health and Ageing, 2006. [http://www.osteoporosis.org.au/files/internal/oa\\_calcvitd\\_gp.pdf](http://www.osteoporosis.org.au/files/internal/oa_calcvitd_gp.pdf) (accessed 3 October 2007).
20. Working Group of the Australian and New Zealand Bone Mineral Society ESAAOA. Med J Aust 2005; 182:281–5.
21. Sambrook PN, Seeman E. Med J Aust 2002;176:S1–S16.
22. O'Neill S, et al. Aust Fam Physician 2004;33:910–7.
23. Sambrook PN, Cooper C. Lancet 2006;367:2010–8.
24. Kanis JA, et al. Osteoporos Int 2005;16:581–9.
25. Servier Laboratories (Australia) Pty Ltd. Protos product information 28 May 2007.
26. O'Donnell S, et al. Cochrane Database Syst Rev 2006;(4):CD005326.
27. European Medicines Evaluation Agency. Protelos European Public Assessment Report. London: EMEA, 2007. <http://www.emea.eu.int/humandocs/Humans/EPAR/protelos/protelos.htm> (accessed 4 April 2007).

Updated October 2007: PBS listing extended to include primary prevention.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

## Correspondence from Servier Laboratories (Australia) Pty Ltd

Servier would like to draw the attention of readers of *NPS RADAR* to the following commentary from the Therapeutics Committee of the Australian and New Zealand Bone & Mineral Society (ANZBMS).

“Strontium ranelate has been shown to reduce the risk of vertebral and non-vertebral fractures in two large trials, in patients with and without fractures at baseline, in postmenopausal women with osteoporosis or osteopenia and in women over 80 years of age. The ANZBMS notes that the effect size on non-vertebral fractures is comparable with the bisphosphonates. The drug reduces fractures within the first 12 months of the beginning of therapy and the benefits are sustained for 5 years. These features make it a first line option, not a second line agent to be used only after other therapy.”

This commentary was written in response to statements about strontium ranelate made by the NPS.

Servier agrees with the ANZBMS commentary and welcomes the decision of the PBS to allow usage of strontium ranelate (Protos) in postmenopausal women without a fracture (aged  $\geq 70$  years, BMD T-score  $\leq -3.0$ ) as well as in postmenopausal women who have already suffered a minimal trauma fracture.

Strontium ranelate (Protos) has marketing approval for treatment of postmenopausal osteoporosis to reduce the risk of fracture. Servier does not suggest use the product in any way incompatible with that described in the Approved Product Information.

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(Continued next page ...)

## NPS reply

The *NPS RADAR* review of strontium ranelate states that it may be used as initial therapy for postmenopausal osteoporosis. However, strontium has limited data for an effect on hip fracture, there is less experience of its use and its long-term safety profile is yet to be established. For these reasons, *NPS RADAR* and other independent reviews<sup>1-3</sup> have recommended strontium as an alternative therapy when alendronate or risedronate are contraindicated or not tolerated.

Evidence that strontium reduces hip fracture risk is limited to a post-hoc analysis of a high-risk subgroup of women (who were  $\geq 74$  years and had a BMD T-score  $\leq -3.0$ ) from the TROPOS trial.<sup>4</sup> Statistically significant differences found in post-hoc subgroup analyses need

to be interpreted with caution as they could be due to chance. Therefore the evidence that strontium reduces hip fracture risk is limited and requires confirmation. There are more robust data to support an effect of alendronate and risedronate on hip fracture risk in postmenopausal women with or without a previous fracture.<sup>5-7</sup> Refer to the *NPS RADAR* review ([www.npsradar.org.au](http://www.npsradar.org.au)) for more information.

There are unpublished 5-year efficacy data for strontium.<sup>8</sup> There are published data for up to 7 years with risedronate,<sup>9</sup> and up to 10 years with alendronate.<sup>10,11</sup> As with any new drug, the full toxicity profile of strontium is yet to be established.

## References

1. Stevenson M, et al. The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Health Technology Assessment, Vol.11, No 4; executive summary. London, 2007. <http://www.hta.nhsweb.nhs.uk/pdfexecs/summ1104.pdf> (accessed 3 September 2007).
2. Anonymous. Strontium ranelate for osteoporosis? Drug Ther Bull 2006;44:29-32.
3. Anonymous. Strontium: postmenopausal osteoporosis: too many unknowns. Prescrire International 2005;14:207-11.
4. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90:2816-22.
5. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.
6. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82.
7. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40.
8. Reginster JY, Meunier PJ, Roux C, et al. Strontium ranelate: an anti-osteoporotic treatment demonstrated vertebral and nonvertebral antifracture efficacy over 5 years in postmenopausal osteoporotic women. International Osteoporosis Foundation Osteoporosis International, 2006; 17 (Suppl 2): OC24.
9. Mellström DD, Sörensen OH, Goemaere S, et al. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int 2004;75:462-8.
10. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006;296:2927-38.
11. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189-99.

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