



For the prevention and treatment of postmenopausal osteoporosis

Committee's Verdict: **CATEGORY A (Q4)**

BNF: 6.4.1.1

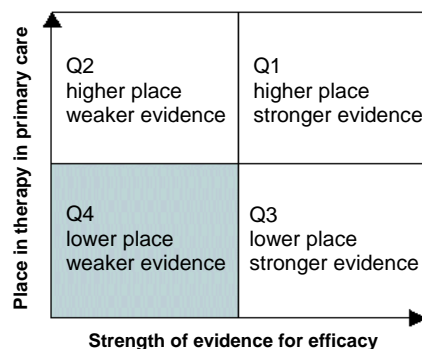
Raloxifene is suitable for prescribing in primary care. However, its use is expected to be second or third-line after other treatments for which there is better evidence.

Category A: suitable for prescribing in primary care

Q4 rating: The evidence for comparative efficacy and safety of raloxifene was considered to be relatively weak, because there was only one robust, placebo-controlled, randomised, controlled trial, the lack of effect on non-vertebral fracture incidence, and the lack of comparisons with bisphosphonates using clinical outcomes. The availability of alternative therapies and adverse effects with raloxifene gave it a relatively low place in therapy.

The Q rating relates to the drug's position on the effectiveness indicator grid.

The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.



MTRAC updated the review of this drug because of new NICE guidance.

Licensed indication

Raloxifene is licensed for the prevention and treatment of osteoporosis in postmenopausal women.¹

Background information

Osteoporosis is characterised by low bone mass with increased fragility and susceptibility to fracture. It results from an imbalance between resorption and regeneration of bone. Its prevalence increases with age, especially in women after menopause because of loss of the protective effect of oestrogen. Other risk factors include smoking, low body-mass index, physical inactivity and long-term corticosteroid use. The National Institute for Health and Clinical Excellence (NICE) estimated that there were about 180,000 symptomatic osteoporotic fractures per year in England and Wales in 2005.²

Severity of osteoporosis is classified by the bone mineral density (BMD) T-score, measured using dual energy X-ray absorptiometry (DXA). This refers to the number of standard deviations from the BMD of an average 25-year-old woman.²

Management of osteoporosis includes addressing lifestyle factors, such as stopping smoking, weight-bearing exercise and adequate intake of calcium and vitamin D.

Pharmacological intervention includes bisphosphonates (alendronate, etidronate, risedronate, ibandronate), hormone replacement

therapy (HRT), teriparatide, strontium ranelate and raloxifene. The bisphosphonates inhibit bone resorption. They may irritate the gastrointestinal tract and need to be taken on an empty stomach. HRT is no longer recommended as first choice therapy for prevention of osteoporosis, because of concerns about its long-term safety. Teriparatide is a recombinant DNA fraction of human parathyroid hormone that stimulates new formation of bone; it is given subcutaneously. Strontium ranelate stimulates bone formation and reduces bone resorption. Raloxifene, a selective oestrogen receptor modulator, also inhibits bone resorption. It has oestrogen agonist effects on bone and the cardiovascular system, and oestrogen antagonist effects on endometrial and breast tissue.

Clinical efficacy

Two RCTs of raloxifene efficacy in postmenopausal osteoporosis have used fractures as an endpoint. One of these, a 12-month trial of 143 women, was not sufficiently powered to detect differences in fracture rates and no differences were seen with raloxifene compared with no treatment.³ The other trial, the Multiple Outcomes of Raloxifene Evaluation (MORE) study, involved 7,705 women.⁴

In the MORE study, osteoporotic postmenopausal women were treated with raloxifene 60 or 120 mg/day for three years, compared with placebo.³ Raloxifene (combined dosage groups) was associated with a relative reduction of 40% in the risk of a new vertebral

fracture, compared with placebo. In the 60 mg raloxifene group, the relative risk was 0.7 (95% CI 0.5 to 0.8, absolute risk reduction = 3.5%, NNT = 29). The reduction in the incidence of fracture with raloxifene was significant regardless of whether women had a fracture at baseline or not. The incidence of non-vertebral fracture did not differ between groups.

After a blinded one-year extension of the MORE trial (n = 5,692), the relative risk of a new vertebral fracture was 0.6 (95% CI 0.5 to 0.8).⁵ After eight years of use, non-vertebral fracture incidence was assessed as a secondary outcome in a separate analysis of 4,011 women from the MORE study; no significant differences were found between raloxifene- and placebo-treated groups.⁶

Two analyses of the three-year MORE data found that changes in BMD during the study did not correlate with the reduction in the risk of fractures with raloxifene, although changes in bone turnover markers did.^{7,8}

Raloxifene 60 mg daily was compared with alendronate 70 mg weekly in two double-blind RCTs (n = 487, 456; duration 12 months).^{9,10} In both studies, alendronate was associated with significantly greater increases in BMD than raloxifene at both spine and hip. Decreases in markers of bone turnover were significantly greater than with raloxifene.

Adverse effects

Adverse events occurring significantly more frequently with raloxifene than placebo in the MORE trial were venous thromboembolic events, hot flushes, influenza-like syndrome, peripheral oedema and leg cramps.³ Treatment with raloxifene was associated with a significantly lower incidence of breast cancer compared with placebo. Findings were similar in the analysis of eight-year data,¹¹ and those observed in other studies of raloxifene. See the Summary of Product Characteristics (SPC) for further details.¹

NICE guidance

A Technology Appraisal on the bisphosphonates (alendronate, etidronate, risedronate), raloxifene and teriparatide for the secondary prevention of osteoporotic fractures in postmenopausal women has been published.² This guidance recommended raloxifene use as an alternative to a bisphosphonate in women for whom the bisphosphonates are contraindicated, or who cannot comply with the special recommendations for their use, or who have

had an unsatisfactory response to or are intolerant of the bisphosphonates.

Additional information

- The recommended dose of raloxifene is 60 mg per day.
- The current cost of one year's treatment with raloxifene 60 mg/day is £259.

References

1. Eli Lilly Ltd. Evista. *Summary of Product Characteristics* 2003.
2. National Institute for Clinical Excellence. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. *Technology Appraisal Guidance* No. 87. 2005.
3. Lufkin E, Whitaker M, Nickelsen T *et al.* Treatment of established postmenopausal osteoporosis with raloxifene. *J Bone Miner Res* 1998;**13**:1747-54.
4. Ettinger B, Black DM, Mitlak B *et al.* Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. *JAMA* 1999;**282**:637-45.
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7. Sarkar S, Mitlak BH, Wong M *et al.* Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. *J Bone Miner Res* 2002;**17**:1-10.
8. Bjarnason NH, Sarkar S, Duong T *et al.* Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. *Osteoporos Int* 2001;**12**:922-30.
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11. Martino S, Disch D, Dowsett SA *et al.* Safety assessment of raloxifene over eight years in a clinical trial setting. *Curr Med Res Opin* 2005;**21**:1441-52.

Launch date: August 1998

Manufacturer: Eli Lilly Ltd

EU/1/98/073/001-4

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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(THIS VERDICT AND SUMMARY SHEET REPLACES VS & SS00/28)



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