

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal Consultation Document

Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

The Department of Health and the National Assembly for Wales have asked the National Institute for Health and Clinical Excellence (NICE or the Institute) to conduct an appraisal of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women and provide guidance on their use to the NHS in England and Wales. The Appraisal Committee has had its first meeting to consider both the evidence submitted and the views put forward by the representatives nominated for this appraisal by professional organisations and patient/carer and service user organisations. The Committee has developed preliminary recommendations on the use of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

This document has been prepared for consultation with the formal consultees. It summarises the evidence and views that have been considered and sets out the preliminary recommendations developed by the Committee. The Institute is now inviting comments from the formal consultees in the appraisal process (the consultees for this appraisal are listed on the NICE website, www.nice.org.uk).

Note that this document does not constitute the Institute's formal guidance on this technology. The recommendations made in Section 1 are preliminary and may change after consultation.

The process the Institute will follow after the consultation period is summarised below. For further details, see the *Guide to the Technology Appraisal Process* (this document is available on the Institute's website, www.nice.org.uk).

- The Appraisal Committee will meet again to consider the original evidence and this Appraisal Consultation Document in the light of the views of the formal consultees.
- At that meeting, the Committee will also consider comments made on the document by people who are not formal consultees in the appraisal process.
- After considering feedback from the consultation process, the Committee will prepare the Final Appraisal Determination (FAD) and submit it to the Institute.

- Subject to any appeal by consultees, the FAD may be used as the basis for the Institute's guidance on the use of the appraised technology in the NHS in England and Wales.

The key dates for this appraisal are:

Closing date for comments: 21 October 2005

Second Appraisal Committee meeting: 1 November 2005

Details of membership of the Appraisal Committee are given in Appendix A and a list of the sources of evidence used in the preparation of this document is given in Appendix B.

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1 Appraisal Committee's preliminary recommendations

This guidance covers the secondary prevention of osteoporotic fragility fractures in postmenopausal women who have sustained a clinically apparent osteoporotic fracture.

This guidance covers the treatment of postmenopausal women who have normal levels of calcium and/or vitamin D. Unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake and are vitamin D replete, calcium and/or vitamin D supplementation should be provided.

This guidance does not cover the treatment of corticosteroid-induced osteoporosis in women who are on systemic long-term corticosteroid therapy.

T-score relates to measurement of bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA) scanning at the femoral neck.

1.1 Bisphosphonates (alendronate, etidronate and risedronate) are recommended as treatment options for the secondary prevention of osteoporotic fragility fractures:

- in women aged 75 years and older, without the need for DXA scanning
- in women aged between 65 and 74 years if the presence of osteoporosis is confirmed by DXA scanning, and
- in postmenopausal women younger than 65 years of age, if they have a very low BMD, that is with a T-score of approximately -3 SD or below* established by a DXA scan, **or** if they have confirmed osteoporosis plus one, or more, additional clinical risk factors: parental history of hip

* For T-score definition, see Sections 2.3 and 2.4

fracture and medical conditions independently associated with bone loss, such as rheumatoid arthritis.

- 1.2 In choosing which bisphosphonate to use, clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients.
- 1.3 Strontium ranelate is recommended as an alternative treatment option, under the circumstances specified in Section 1.1 in women:
- for whom bisphosphonates are contraindicated (see Summaries of Product Characteristics), **or**
 - who are unable to comply with the special instructions for the administration of bisphosphonates, **or**
 - who have had an unsatisfactory response to bisphosphonates (as defined in Section 1.6), **or**
 - who are intolerant of bisphosphonates (as defined in Section 1.7).
- 1.4 Raloxifene is recommended as an alternative treatment option under the circumstances specified in Section 1.1, in women who are unable to take bisphosphonates (as specified in Section 1.3) and:
- for whom strontium ranelate is contraindicated (see Summaries of Product Characteristics), **or**
 - who have had an unsatisfactory response to strontium ranelate (as defined in Section 1.6), **or**
 - who are intolerant of strontium ranelate (as defined in Section 1.8).
- 1.5 Teriparatide is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in women aged 65 years and older who have had an unsatisfactory response to bisphosphonates or intolerance to bisphosphonates, (as defined in 1.6 and 1.7, respectively), **and**
- who have an extremely low BMD (with a T-score of approximately -4 SD or below), **or**

- who have a very low BMD (with a T-score of approximately -3 SD or below) plus multiple fractures (that is, more than two) plus one, or more, additional clinical risk factors: parental history of hip fracture and medical conditions independently associated with bone loss, such as rheumatoid arthritis.

- 1.6 For the purpose of this guidance, an unsatisfactory response occurs when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is also evidence of a decline in BMD below her pre-treatment baseline.
- 1.7 For the purpose of this guidance, intolerance of bisphosphonates is defined as oesophageal ulceration, erosion or stricture, any of which is sufficiently severe to warrant discontinuation of treatment with a bisphosphonate.
- 1.8 For the purpose of this guidance, intolerance of strontium ranelate is defined as persistent nausea or diarrhoea, either of which warrants discontinuation of treatment with strontium ranelate.

2 Clinical need and practice

- 2.1 Osteoporosis is a progressive, systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.
- 2.2 Bone formation exceeds bone resorption in youth, but by the third decade of life there is a gradual loss of bone mass. Osteoporosis is therefore usually an age-related disease. It can affect both sexes, but women are at greater risk because bone loss is accelerated, to a variable degree, after the menopause because of a decrease in oestrogen production.
- 2.3 Diagnosis of osteoporosis is based on the measurement of BMD, with reference to the number of standard deviations (T-score) from the BMD in an average 25-year-old woman:

- normal: T-score of -1 or above
 - osteopenia: T-score of between -1 and -2.5
 - osteoporosis: T-score of -2.5 or below
 - established/severe osteoporosis: T-score of -2.5 or below with one or more associated fractures.
- 2.4 T-score measurements vary by site and method. It has been recommended that BMD should be measured at the femoral neck using DXA to estimate fracture risk.
- 2.5 It has frequently been quoted that over 2 million women have osteoporosis (that is, have a T-score below -2.5 SD) in England and Wales. However, recent epidemiological data based on a UK sample indicate that this figure may be closer to 1.1 million. Osteoporosis is most common in older white women. Prevalence of osteoporosis increases markedly with age after menopause from approximately 2% at 50 years of age rising to over 25% at 80 years.
- 2.6 Fragility fracture is the clinically apparent and relevant outcome in osteoporosis (referred to as 'fracture' or 'osteoporotic fracture' in the following). In the absence of fracture the condition is asymptomatic and often remains undiagnosed. Osteoporotic fractures occur most commonly in the vertebrae, hip and wrist, and are associated with substantial disability, pain and reduced quality of life.
- 2.7 In women aged over 50 years, the lifetime risk of a vertebral fracture is estimated to be one in three, and one in five for hip fracture. Postmenopausal women with an initial fracture are at substantially greater risk of subsequent fractures. For instance, a woman with a vertebral fracture has an increased relative risk (RR) of 4.4 for a further vertebral fracture, 2.3 for a hip fracture, and 1.4 for a wrist fracture.
- 2.8 It is estimated that annually there are 180,000 osteoporosis-related symptomatic fractures in England and Wales. Of these, 70,000 are hip

fractures, 25,000 are clinical vertebral fractures, and 41,000 are wrist fractures.

- 2.9 After a hip fracture, a high proportion of women are permanently unable to walk independently or perform other activities of daily living and, consequently, many are unable to live independently. Hip fractures are also associated with increased mortality; estimates of the relative mortality risk vary from 2 to greater than 10 in the 12 months following hip fracture. However, it is unclear to what extent this can be attributed to fracture alone as opposed to pre-existing comorbidity.
- 2.10 Vertebral fractures are associated with loss of height and curvature of the spine and result in pain, breathing difficulties, gastrointestinal problems and difficulties performing activities of daily living. It is thought that the majority of vertebral fractures (50–70%) do not come to clinical attention. Vertebral fractures are also associated with increased mortality; UK-specific data indicate a 4.4-fold increase in mortality due to vertebral fractures. However, as with hip fractures, it is unclear to what extent this may be due to comorbidities.
- 2.11 In addition to increasing age and low BMD, other clinical factors have been associated with an increased fracture risk, such as prior fracture, parental history of hip fracture; low body mass index (in the absence of knowledge about BMD and defined as less than 19 kg/m²); long-term systemic use of corticosteroids and medical conditions independently associated with bone loss such as rheumatoid arthritis. A full review of risk factors associated with osteoporotic fracture has been carried out for the development of the NICE Clinical Guideline *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk*.
- 2.12 Under the auspices of the World Health Organization (WHO), an algorithm is currently being developed that quantifies the absolute risk of osteoporotic fracture on the basis of risk factors.

3 The technologies

Bisphosphonates: alendronate, etidronate, risedronate

- 3.1 Bisphosphonates are inhibitors of bone resorption and increase BMD by altering osteoclast activation and function. Alendronate, etidronate and risedronate are licensed in the UK for the management of osteoporosis.
- 3.2 Alendronate (Merck Sharp & Dohme Ltd) is an oral bisphosphonate licensed in the UK at a dose of 10 mg/day for the treatment of osteoporosis in postmenopausal women to prevent fractures. A once-weekly preparation (70 mg) is also licensed for the treatment of postmenopausal osteoporosis. Prices are £23.12 for 28 10-mg tablets and £22.80 for four 70-mg tablets (excluding VAT; *British National Formulary* 49th edition [BNF 49]). This equates to £301.38 per annum for the once daily treatment or £297.21 per annum for the once weekly treatment. Costs may vary in different settings because of negotiated procurement discounts.
- 3.3 Etidronate (Procter & Gamble Pharmaceuticals UK Ltd) is an oral bisphosphonate licensed in the UK for the treatment of osteoporosis. The drug is administered in 90-day cycles, with each cycle consisting of etidronate (400 mg daily) for 14 days followed by calcium carbonate (1.25 g daily) for the remaining 76 days. The price per 90-day pack is £37.39 (excluding VAT; *BNF* 49), which equates to £151.64 per annum. Costs may vary in different settings because of negotiated procurement discounts.
- 3.4 Risedronate (Procter & Gamble Pharmaceuticals UK Ltd) is an oral bisphosphonate licensed in the UK at a dose of 5 mg/day and at 35 mg/week for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures, and for the treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. Prices are £19.10 for 28 5-mg tablets and also £20.30 for four 35-mg tablets (excluding VAT; *BNF* 49), which equates to £248.98 per annum for the daily treatment or £264.63 per

annum for the once weekly treatment. Costs may vary in different settings because of negotiated procurement discounts.

- 3.5 Gastrointestinal side-effects are common with bisphosphonates. In people with oesophageal abnormalities and other factors which delay oesophageal transit or emptying, risedronate should be used cautiously and alendronate is contraindicated. For full details of side effects and contraindications, see the Summaries of Product Characteristics.
- 3.6 Bisphosphonates have relatively complex instructions for administration. Alendronate and risedronate must be taken with 200 ml and 120 ml of water, respectively. Before and immediately after administration patients may not eat or drink, and must remain upright for stipulated time periods. Etidronate should be taken at the midpoint of a 4-hour fast (that is, 2 hours before and 2 hours after food or medication).

Selective oestrogen receptor modulators (SERMs): raloxifene

- 3.7 SERMs are a class of drugs with selective activity in various organ systems, acting as weak oestrogen receptor agonists in some systems and as oestrogen antagonists in others. The aim of treatment with SERMs is to maximise the beneficial effects of oestrogen on bone and to minimise the adverse effects on the breast and endometrium.
- 3.8 Raloxifene (Eli Lilly and Company Ltd) is the only SERM licensed for the treatment of osteoporosis in postmenopausal women. The recommended dose is 60 mg/day. The prices of 28- and 84-tablet packs are £19.86 and £59.59, respectively (excluding VAT; *BNF 49*), which equates to £258.89 per annum. Costs may vary in different settings because of negotiated procurement discounts.
- 3.9 Raloxifene is contraindicated in people with a history of venous thromboembolism, hepatic impairment, cholestasis, severe renal impairment, undiagnosed uterine bleeding, and endometrial cancer. Raloxifene should not

be co-administered with systemic oestrogens and, in patients with breast cancer, it should not be used for osteoporosis treatment and prevention until treatment of the breast cancer, including adjuvant therapy, has been completed. Raloxifene is associated with an increased risk of venous thromboembolic events, particularly during the first 4 months of treatment, which is similar to the reported risk associated with hormone replacement therapy. For full details of side effects and contraindications, see the Summary of Product Characteristics.

Strontium ranelate

- 3.10 Strontium ranelate (Servier Laboratories Ltd) is composed of two atoms of stable strontium (an element with properties similar to calcium) and one molecule of ranelic acid. It is thought to have a dual effect on bone metabolism, increasing bone formation and decreasing bone resorption. It is licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. The recommended dose is one 2 g sachet/day, taken as a suspension in water. The price of a 28-sachet pack is £25.60 (excluding VAT; *BNF 49*), which equates £333.71 per annum. Costs may vary in different settings because of negotiated procurement discounts.
- 3.11 The absorption of strontium ranelate is reduced by food, milk and derivative products. It should therefore be administered between meals, preferably at bedtime or at least 2 hours after eating.
- 3.12 Strontium ranelate is not recommended in patients with severe renal impairment and should be used with caution in patients at increased risk of venous thromboembolism. Treatment with strontium ranelate should be discontinued during treatment with oral tetracycline or quinolone antibiotics. For full details of side effects and contraindications, see the Summary of Product Characteristics.

Parathyroid hormone: teriparatide

- 3.13 Teriparatide (Eli Lilly and Company Ltd) is a recombinant, fragment of human parathyroid hormone and, as an anabolic agent, it stimulates new formation of bone, and increases resistance to fracture.
- 3.14 Teriparatide was approved in the UK for the treatment of established osteoporosis in postmenopausal women in June 2003. The recommended dose is 20 micrograms administered once daily by subcutaneous injection in the thigh or abdomen. Patients taking teriparatide must receive training on the injection technique. The maximum total duration of treatment is restricted, by the licence, to 18 months. The price of a 28-day pre-filled pen is £271.88 (excluding VAT; *BNF 49*), which is equal to £3544.15 per annum. Costs may vary in different settings because of negotiated procurement discounts.
- 3.15 Particular contraindications include pre-existing hypercalcaemia, severe renal impairment, metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone), unexplained elevations of alkaline phosphatase, and previous radiation therapy to the skeleton. For full details of side effects and contraindications, see the Summary of Product Characteristics.

4 Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

- 4.1.1 The Assessment Report reviewed data from published randomised controlled trials (RCTs) in postmenopausal women where fracture or health-related quality of life was an endpoint and where one of the six drugs of interest was compared with a relevant comparator including: no treatment, placebo, or one of the other included interventions. The majority of studies used placebo or no treatment as a control. Most studies ensured that women in all arms had

normal calcium levels or adequate supplementation, and some studies also required additional dietary supplementation with vitamin D.

4.1.2 For this appraisal, reductions in RRs associated with treatment were pooled regardless of the baseline BMD and fracture status of the participants in the studies. It was also assumed that these reductions in RR remain constant at all ages although there was little evidence for the effectiveness of the drugs in women aged 80 years and older.

4.1.3 For vertebral fractures, some studies used clinical (that is, symptomatic) fractures as their endpoint while others used fractures that were identified radiographically; such fractures, which are termed radiographic or morphometric, include both symptomatic and asymptomatic fractures. Various definitions of radiographic fractures have been developed, but those definitions that require a 20% reduction in vertebral height are generally recognised as producing more accurate results than those that require a 15% reduction.

4.1.4 For non-vertebral fracture types, individual data on hip, leg, pelvis, wrist, hand, foot, rib and humerus were sometimes provided, while some studies only presented data for all non-vertebral fractures grouped together.

4.1.5 **Alendronate**

4.1.5.1 Sixteen RCTs of alendronate in postmenopausal women were included in the Assessment Report: two studies in women with low or normal BMD; one in women with osteopenia; eight in women with osteopenia or osteoporosis; four in women with osteoporosis; and one in women with established osteoporosis. Overall, 15 studies compared alendronate with placebo or with no treatment; and two used active comparators. All the studies were conducted in women who had adequate levels of calcium from dietary intake or were receiving calcium supplementation.

- 4.1.5.2 Two studies, one comparing alendronate with oestrogen or oestrogen/alendronate combined and the other comparing alendronate with teriparatide, found no statistically significant differences in clinically apparent fractures of any type in women with osteoporosis. However, back pain was reported less frequently by women in the teriparatide group compared with women in the alendronate group (6% vs 19%, $p = 0.012$).
- 4.1.5.3 In addition to the 16 RCTs, a 2-year study demonstrated the equivalence of weekly and daily doses of alendronate, in terms of clinical fracture incidence and gastrointestinal adverse events. However, this study was not included in the analysis, as it did not have the specified comparators.
- 4.1.5.4 The meta-analysis for alendronate relative to placebo, carried out by the Assessment Group resulted in an RR of vertebral fracture of 0.56 (95% confidence interval [CI] 0.46 to 0.68, 4 RCTs, $n = 7039$); an RR of hip fracture of 0.62 (95% CI, 0.40 to 0.98, 4 RCTs, $n = 7881$), an RR of wrist fracture of 0.67 (95% CI, 0.34 to 1.31, 4 RCTs, $n = 7931$) and an RR for other non-vertebral fractures of 0.81 (95% CI, 0.68 to 0.97; 6 RCTs, $n = 9973$).
- 4.1.5.5 Gastrointestinal adverse events including nausea, dyspepsia, mild oesophagitis/gastritis and abdominal pain were reported in at least one third of the participants in studies of alendronate. However, only one study found the increased frequency of these symptoms to be statistically significant relative to placebo. This is consistent with post-marketing studies indicating that around one-third of alendronate users experience gastrointestinal adverse events. In order to avoid oesophagitis, the Summary of Product Characteristics now recommends that alendronate should be taken, upon rising for the day, with a full glass of water. It is possible that these instructions were not followed in all of the studies, particularly the earlier ones.
- 4.1.5.6 One study reported health-related quality of life outcomes. At 12 months there were statistically significant improvements in the alendronate group

but not in the control group in scores for pain, social isolation, energy level and physical ability.

4.1.6 **Etidronate**

- 4.1.6.1 Twelve RCTs of etidronate in postmenopausal women were reviewed: three studies in women with low-to-normal BMD; two in women with osteopenia or osteoporosis; one in women with osteoporosis; one in women with osteoporosis and established osteoporosis, and five in women with established osteoporosis. Four studies included active comparators, and eight compared etidronate with placebo or with no treatment (although in six of these, subjects in all arms received calcium, either alone or with vitamin D). Some studies did not use the exact treatment regimen currently licensed in the UK (that is, 90-day cycle comprising 400 mg etidronate for 14 days, followed by calcium carbonate 1.25 g for the remaining 76 days). None of the studies reported health-related quality of life outcomes.
- 4.1.6.2 The meta-analysis of RCTs for etidronate relative to placebo, carried out by the Assessment Group resulted in an RR of vertebral fracture of 0.40 (95% CI, 0.20 to 0.83, 3 RCTs, n = 341); an RR of hip fracture of 0.50 (95% CI, 0.05 to 5.34, 2 RCTs, n = 180), and an RR for other non-vertebral fractures of 1.04 (95% CI, 0.64 to 1.69; 5 RCTs, n = 490). There were no data for wrist fracture.
- 4.1.6.3 An observational study in a general practice setting in the UK reported on fracture rates in people with a diagnosis of osteoporosis who were receiving cyclical etidronate compared with those who were not taking a bisphosphonate. People taking etidronate had an RR of non-vertebral fracture of 0.80 (95% CI, 0.70 to 0.92). The RR risk of hip fracture was 0.66 (95% CI, 0.51 to 0.85) and that of wrist fracture 0.81 (95% CI, 0.58 to 1.14).

4.1.6.4 Higher rates of gastrointestinal adverse effects were found in the etidronate groups of four RCTs, although the differences were not always statistically significant. However, non-RCT evidence and testimonies from clinical experts and patient experts suggested that etidronate may be associated with fewer gastrointestinal adverse effects than are other bisphosphonates.

4.1.7 **Risedronate**

4.1.7.1 Seven RCTs in postmenopausal women were reviewed: one study in women with normal BMD; one in women with osteopenia; one in women with osteopenia or osteoporosis; one in women with osteoporosis or specific risk factors for hip fracture such as a recent fall; and three in women with established osteoporosis. All compared risedronate with placebo (although, with the exception of those in the normal BMD study, all women also received calcium) and none reported on health-related quality of life.

4.1.7.2 The meta-analysis for risedronate relative to placebo, carried out by the Assessment Group resulted in an RR of vertebral fracture of 0.61 (95% CI, 0.50 to 0.75, 3 RCTs, n = 2301); an RR of hip fracture of 0.74 (95% CI, 0.59 to 0.93, 3 RCTs, n = 11,770), an RR of wrist fracture of 0.68 (95% CI, 0.43 to 1.08, 2 RCTs, n = 2439) and an RR for other non-vertebral fractures of 0.76 (95% CI, 0.64 to 0.91; 5 RCTs, n = 12,399).

4.1.7.3 Overall and gastrointestinal adverse events were similar in the risedronate and placebo groups in all of the studies.

4.1.8 **Raloxifene**

4.1.8.1 Three RCTs of raloxifene in postmenopausal women were identified, but only two were included in the Assessment Group's meta-analysis: the largest study (the Multiple Outcomes of Raloxifene Evaluation study – MORE) was in women with osteoporosis, of whom 37% had a vertebral

fracture at entry, and a smaller study was in women all of whom had established osteoporosis. Both compared raloxifene with placebo (in both studies, women in both arms received calcium and vitamin D). Both studies examined raloxifene at doses of 60 mg/day (UK licensed dose for treatment of postmenopausal osteoporosis) and 120 mg/day. Neither reported on health-related quality of life. The mean age in the studies was 67–68 years. The MORE study was extended to further assess fracture, breast cancer, and cardiovascular and uterine safety outcomes. A third study examined the additive effect of raloxifene, compared with placebo, in women with a femoral neck T-score of –2.0 or lower, with or without prior fracture, who were also receiving fluoride, calcium and vitamin D. Because of the use of fluoride as a co-intervention, these results were not included in the Assessment Group's meta-analysis.

- 4.1.8.2 The meta-analysis for raloxifene relative to placebo, carried out by the Assessment Group resulted in an RR of vertebral fracture of 0.65 (95% CI, 0.53 to 0.79, 1 RCT, n = 4551); an RR of hip fracture of 1.13 (95% CI, 0.66 to 1.96, 2 RCTs, n = 6971), an RR of wrist fracture of 0.89 (95% CI, 0.68 to 1.15, 1 RCT, n = 6828) and an RR for other non-vertebral fractures of 0.92 (95% CI, 0.79 to 1.07; 1 RCT, n = 6828).
- 4.1.8.3 The most serious adverse effect associated with raloxifene is the approximately three-fold increased risk of venous thromboembolism. Statistically significantly higher incidences of hot flushes, arthralgia, dizziness, leg cramps, influenza-like symptoms, endometrial cavity fluid, peripheral oedema and worsening diabetes were also found with raloxifene compared with placebo.
- 4.1.8.4 The MORE study shows that raloxifene protects against breast cancer, with the RR at 4 years, of all types of breast cancer, reported as 0.38 (95% CI, 0.24 to 0.58) and for invasive breast cancer as 0.28 (95% CI, 0.17 to 0.46). The impact of raloxifene on cardiovascular disease is

unclear, although there is evidence that it lowers fibrinogen and both total and LDL cholesterol without increasing HDL cholesterol.

4.1.9 **Strontium ranelate**

- 4.1.9.1 Three RCTs of strontium ranelate in postmenopausal women were identified: one study in women with osteoporosis and two in women with osteoporosis or established osteoporosis. All three studies compared strontium ranelate against placebo. All three studies provided calcium and vitamin D supplementation to ensure an adequate intake.
- 4.1.9.2 The Assessment Group reported the results of a published meta-analysis which resulted in an RR for vertebral fracture of 0.60 (95% CI 0.53 to 0.69, 2 RCTs, n = 6551); and an RR for all non-vertebral fractures (including wrist fracture) of 0.84 (95% CI 0.73 to 0.97, 2 RCTs, n = 6551). Hip fracture efficacy was established in one study: The RR for hip fracture in the whole study population was 0.85 (95% CI 0.61 to 1.19, 1 RCT, n = 4932). A post-hoc subgroup analysis in women over 74 years of age and with a T-score of -2.4 SD resulted in an RR for hip fracture of 0.64 (95% CI 0.41 to 0.98, 1 RCT, n = 1977).
- 4.1.9.3 In general, strontium ranelate was not associated with an increased risk of adverse effects and for the most part adverse effects were mild and transient. Transient nausea, diarrhoea and creatine kinase elevations were the most commonly reported clinical adverse effects. A serious adverse event associated with strontium ranelate therapy was an increased incidence (RR = 1.42) of venous thromboembolism (VTE) and pulmonary embolism. This is being addressed with the extension of ongoing studies and by post-marketing surveillance.
- 4.1.9.4 One study published results on health-related quality of life. Strontium ranelate was said to benefit quality of life when compared with placebo, as assessed by the QUALIOST osteoporosis-specific questionnaire and by the General Health perception score of the SF-36 general scale.

4.1.10 **Teriparatide**

- 4.1.10.1 Three RCTs of teriparatide in postmenopausal women were considered: one study compared teriparatide with alendronate in women with osteoporosis (but was not targeted at women with fractures), and two were placebo-controlled (although subjects also received vitamin D either with calcium or with nutritional advice to ensure adequate calcium intake). The largest trial was conducted in women with established osteoporosis, and the second in women who either had established osteoporosis or had osteoporosis and had been receiving hormone replacement therapy for at least 2 years.
- 4.1.10.2 For vertebral fractures (using a 20% reduction in vertebral height as the fracture definition) and grouped non-vertebral fractures in women with established osteoporosis, the main placebo-controlled RCT found RRs of 0.35 (95% CI, 0.22 to 0.55) and 0.65 (95% CI, 0.43 to 0.98), respectively, in favour of teriparatide. When considered separately, the study did not demonstrate that teriparatide prevents hip and wrist fractures in women with established osteoporosis (RR for hip fractures 0.5; 95% CI, 0.09 to 2.73, RR for wrist fractures 0.54; 95% CI, 0.22 to 1.35). In this main placebo-controlled trial teriparatide reduced the incidence of new or worsened back pain reported as an adverse event.
- 4.1.10.3 Data from a follow-up observational study cited in the manufacturer's submission (published in abstract form or available as unpublished manuscript only) suggest that 18 months after the end of treatment with teriparatide there was a 41% reduction in vertebral fracture risk compared with placebo ($p = 0.004$). Further data from the same study 31 months after end of treatment with teriparatide suggest that proportionally fewer women who had received teriparatide reported non-vertebral fractures compared with those who had received placebo (13.3% in the placebo group; 8.5% in the 20 micrograms/day teriparatide group; 7.3% in the 40 micrograms/day teriparatide group; $p = 0.03$ for both treatment groups).

versus placebo). No information was given on vertebral fractures for the 31-month follow up.

- 4.1.10.4 The study comparing 40 micrograms/day teriparatide (twice the licensed dose) with 10 mg/day alendronate found an RR of non-vertebral fracture in women with osteoporosis of 0.30 (95% CI, 0.09 to 1.05). The study did not provide data on vertebral fractures. Back pain was reported less frequently in the teriparatide group (6% vs 19%, $p = 0.012$).
- 4.1.10.5 Nausea and headaches occurred more frequently with 40 micrograms/day teriparatide in the main placebo-controlled trial. In the smaller placebo-controlled trial, a proportion of women taking teriparatide were reported to suffer mild discomfort at the injection site. A systematic review of parathyroid hormone reported that treatment in a small proportion of women was associated with hypercalcaemia.
- 4.1.10.6 The main placebo-controlled RCT reported that adherence with injections varied from 79% to 83% and that there were no statistically significant differences between the teriparatide and placebo groups. The smaller placebo-controlled trial found that, after 3 years, 78% of women receiving teriparatide completed treatment, compared with 100% on placebo.

4.2 Cost effectiveness

The Assessment Group's economic model

- 4.2.1 The Assessment Group provided an updated cost–utility model in which the cost effectiveness of the individual drugs was estimated for women at different levels of annual absolute risk of fracture and different ages (from age 50, in 5-year age bands). This was done because the cost-effectiveness of interventions at a given age is not only determined by total absolute fracture risk, but also by the proportion of fractures at each site within a given absolute risk, the mortality hazard over the treatment period, the baseline utility values and the probability of entering a nursing home with associated cost and utility consequences.

- 4.2.2 The RR reductions for fracture were taken from the meta-analyses described above. Based on the advice from the Guideline Development Group, it was assumed that RRs remain constant across all ages, T-scores and fracture status.
- 4.2.3 All osteoporotic fractures were included in the modelling. The RR for hip fracture was assumed to apply also to pelvis and other femoral fractures. The RR for non-vertebral fracture was assumed to apply to proximal humerus, rib, sternum, scapula, tibia, fibula and wrist fracture. Where confidence intervals spanned unity, no effect was assumed. For strontium ranelate, however, a non-significant RR for hip fracture was used in order to acknowledge a statistically significant effect seen in a subgroup of older women. For teriparatide, modelling was carried out including and excluding the non-significant hip fracture effect. The model used UK-specific epidemiological data on femoral neck BMD.
- 4.2.4 The model assumed an initial utility in the year of fracture and a higher utility in subsequent years. The time horizon was 10 years consisting of 5 years treatment with sustained efficacy plus 5 years linear decline to no effect. The percentage of women that are assumed to move from community living to a nursing home following a hip fracture increased with increasing age. An age-dependent gradient of hip fracture risk was used. An association between vertebral or proximal humerus fracture and increased mortality in osteoporotic patients was included. No follow-up BMD scans were included in the model, reflecting clinical practice in the UK, based on the limited DXA availability.
- 4.2.5 A number of clinical risk factors were aggregated and quantified as absolute risk. The model used a fracture-risk algorithm derived from a study carried out under the auspices of the WHO. This study analysed the effect of age, sex, T-score and several other clinical risk factors on fracture incidence in 12 cohorts from Europe, North America and Asia, with a total of 60,000 people and 250,000 patient-years of observation. The risk factors included body mass index, previous fracture, ever use of corticosteroids, parental history of

fracture, current smoking, alcohol intake of more than 2 units per day, and rheumatoid arthritis. The study provided prevalence data for the different risk factors, and risk ratios for hip fracture and osteoporotic fracture for each risk factor, including T-score and age. From these risk ratios an algorithm was developed that integrates all risk factors into absolute risk of fracture.

4.2.6 A woman with a T-score of -2.5 and a prior fracture has an absolute annual risk of fracture of 1.7% at the age of 50-54, rising to 4.1% at the age of 80-84. A woman aged 65-69 with a prior fracture has an absolute annual risk of fracture of 1.3% at a T-score of -1 rising to 9.7% at a T-score of -5 . A 50-54 year old woman with a prior fracture and a T-score of -4 has a similar absolute annual risk of fracture (4.4%) to an 80-84 year old woman with a T-score of -2.5 (4.1%).

4.2.7 The estimates of cost effectiveness were generated for different levels of absolute risk derived from a large number of combinations of T-scores, ages and risk factors. For practical reasons relating to the number of potential combinations, only single-point RRs of fracture calculated from the log-normal efficacy distributions were used in the model.

4.2.8 For raloxifene, the cost effectiveness was modelled both including and excluding the breast cancer benefit. Four-year follow-up data from the MORE study were used, and it was assumed that women with low BMD have a lower breast cancer risk than women with normal BMD. Due to the small absolute risk of venous thrombosis in women, and the non-significant effect on cardiovascular events for all women, neither effect was incorporated into the model.

Costs per quality-adjusted life-year (QALY)

4.2.9 The cost per quality-adjusted life-year gained compared with no treatment (CQG) became more favourable with increasing age and decreasing T-score, that is with increasing annual absolute risk of fracture (abbreviated to 'risk' in the following) for the bisphosphonates, strontium ranelate and

teriparatide. This was also the case for raloxifene, when the breast cancer benefit was excluded. However, when the breast cancer benefit for raloxifene was included, the CQG became less favourable with increasing risk.

- 4.2.10 Alendronate is taken as a proxy for the bisphosphonates because the data for alendronate generally provide the best case in terms of cost effectiveness.
- 4.2.11 For women aged 60-64 with a T-score of -2.5 and a prior fracture (equivalent to a risk of 1.83%), the CQG was £42,000 for alendronate, £140,000 and £25,000 for raloxifene (excluding and including the breast cancer benefit respectively), £72,000 for strontium ranelate and £161,000 for teriparatide. For women aged 60-64 with a T-score of -3.5 and a prior fracture (equivalent to a risk of 3.11%), the CQG was £15,000 for alendronate, £105,000 and £29,000 for raloxifene (excluding and including the breast cancer benefit respectively), £36,000 for strontium ranelate and £78,000 for teriparatide.
- 4.2.12 For women aged 65-69 with a T-score of -2.5 and a prior fracture (equivalent to a risk of 2.29%), the CQG was £32,000 for alendronate, £85,000 and £26,000 for raloxifene (excluding and including the breast cancer benefit respectively), £53,000 for strontium ranelate and £126,000 for teriparatide. For women aged 65-69 with a T-score of -4 and a prior fracture (equivalent to a risk of 4.99%), the CQG was £5,000 for alendronate, £52,000 and £27,000 for raloxifene (excluding and including the breast cancer benefit respectively), £18,000 for strontium ranelate and £44,000 for teriparatide.
- 4.2.13 For women aged 75-79 with a T-score of -2.5 and a prior fracture (equivalent to a risk of 3.58%), the CQG was £16,000 for alendronate, £46,000 and £27,000 for raloxifene (excluding and including the breast cancer benefit respectively), £29,000 for strontium ranelate and £70,000 for teriparatide. For women aged 75-79 with a T-score of -4 and a prior fracture

(equivalent to a risk of 7.38%), the CQG was £1,000 for alendronate, £26,000 and £21,000 for raloxifene (excluding and including the breast cancer benefit respectively), £10,000 for strontium ranelate and £27,000 for teriparatide.

4.2.14 Clinical risk factors other than age and T-score also contribute to the risk of fracture. Although absolute risk of fracture provides an overall measure of fracture risk, the economic modelling revealed that absolute risk is not a precise indicator of cost effectiveness. This is because absolute risk covers all fracture sites included in the analysis, but different fracture sites have different impacts on quality of life, costs and mortality; the ratio of the risks for hip to non-hip fracture changes with age; different risk factors have different effects on hip and non-hip fractures, and this effect changes with age. Absolute risk intervention thresholds therefore differ slightly for each individual risk factor and for each risk factor combination. Every possible combination of age, T-score and risk factor(s) has its own intervention threshold. The clinical risk factors included in the modelling were current smoking, alcohol intake of more than 2 units per day, ever use of corticosteroids, parental history of hip fracture and rheumatoid arthritis.

Manufacturers' models

4.2.15 For alendronate, the manufacturer's model resulted in a CQG of £3135 for 70-year-old women with a T-score below -1.6 SD. The manufacturer's model gave more favourable CQG values than the Assessment Group's model. This could be because of different assumptions used for baseline fracture prevalence (not adjusted in the manufacturer's model), different utilities for vertebral fractures and efficacy data, different risk groups used, or the longer time horizon used in the manufacturer's model.

4.2.16 For etidronate, the manufacturer calculated a CQG of £18,634 for 70-year-old women with a T-score below -2.5 SD.. The manufacturer's model included morphometric vertebral fractures and corticosteroid use as risk factors for

further fractures. It is unclear whether the manufacturer's CQG figure was for women with or without osteoporotic fragility fracture.

4.2.17 For risedronate, the manufacturer provided data from two models. The CQG derived from the manufacturer's own model was £577 for age 74. However, in the second model provided by the manufacturer, which was commissioned from an external body, the CQG was higher, varying from £35,800 at age 60 to £4800 at age 80 for women with a prior vertebral osteoporotic fragility fracture and a T-score of -2.5 . For women at slightly higher risk, the CQGs were £18,600 or less for all age groups. The CQG figure calculated by the manufacturer's own model is difficult to substantiate from the information given. The CQG figures generated by the second model are more consistent with the figures provided by the Assessment Group's model though they do differ somewhat. This may be due to differing cost and RR inputs.

4.2.18 For raloxifene, the manufacturer provided data, all including the breast cancer benefit, for different age groups and different risk levels. It was not clear how the different risk levels were defined. The CQG figures varied from £12,000 to £22,000. The manufacturer's results were slightly more favourable than the Assessment Group's analysis, even when the Assessment Group included the breast cancer benefit. In the Assessment Group's model, the RR for the breast cancer effect was higher (0.38) than the RR of invasive breast cancer used in the manufacturer's model (0.28) and the breast cancer risk was adjusted for the association between low BMD and decreased risk of breast cancer. Additionally, the manufacturer's model used different assumptions for baseline fracture prevalence (not adjusted in the manufacturer's model), different utilities for vertebral fractures, different efficacy data, different risk groups, and a longer time horizon.

4.2.19 The manufacturer of strontium ranelate provided two models: one developed in-house and the other commissioned from an external body. For women aged over 75 with previous fractures and a T-score of -2.5 , the manufacturer's own model showed that strontium ranelate was cost-effective

at a maximum acceptable incremental cost effectiveness ratio of £30,000 per QALY. The results of the manufacturer's model are comparable with those generated by the Assessment Group's model. The externally developed model resulted in a CQG of £6,341 for 70 year old women with a previous vertebral fracture and a T-score of -2.5, decreasing to £5,002 at age 80. These manufacturer's results were more favourable than the Assessment Group's results because different modelling assumptions were used.. A limited number of health state transition possibilities were incorporated. More favourable hip fracture efficacy data from a subgroup of patients aged over 74 were used, along with slightly more favourable efficacy data for wrist and proximal humerus fracture. Higher hip fracture costs were used.

- 4.2.20 The manufacturer of teriparatide provided CQGs for women aged 69 years. For women with fractures which had occurred more than 6 months previously (historical fracture), the CQG was £35,400 and for women with a more recent fracture the CQG was £28,863. The manufacturer supplied additional economic analyses with CQGs of £18,845 and £12,106 for historical and recent fracture, respectively, based on changes to the assumptions of sustained efficacy for non-vertebral fractures and of the RR for specific risk groups. The manufacturer's model and the Assessment Group's model differed in a number of assumptions, such as the baseline fracture prevalence (not adjusted in the manufacturer's model), and different utilities. The Assessment Group's model used more favourable assumptions on the duration of sustained efficacy after the end of treatment.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide, having considered evidence on the nature of the condition and the value placed on the benefits of these drugs by people at risk of secondary osteoporotic fragility fractures, those who represent them,

and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

- 4.3.2 The Committee considered that the selection of individuals for treatment should be based on the inter-related risk factors of age and low BMD, and should also take into account other risk factors. The Committee noted that, since *NICE Technology Appraisal* No. 87, several risk factors had been assessed by the WHO study, as being independent of BMD and their effects on risk were quantified. These were prior fracture, parental history of hip fracture, ever use of corticosteroids, rheumatoid arthritis, current smoking and alcohol intake of more than 2 units per day. The Committee noted that the WHO study also indicated that low BMI was a risk factor, but was not independent of BMD.
- 4.3.3 The Committee was concerned about recommending the use, as risk factors, of current smoking and alcohol intake because their effects on fracture risk were relatively small, and such behavioural risk factors are difficult to confirm reliably. However, the Committee noted that medical conditions which are independently associated with bone loss, such as rheumatoid arthritis, are important for risk assessment. The Committee was also mindful that long-term systemic corticosteroid use, as a principal risk factor, requires separate consideration and is not covered in this guidance, and that a full review of other risk factors was carried out as part of the Clinical Guideline Development.
- 4.3.4 The Committee recognised that asymptomatic vertebral fragility fractures are a risk factor for further fracture, but that women who have such fractures do not present in clinical practice unless they are discovered during routine consultations. This guidance specifically applies to women who present with clinically apparent fractures identified directly by symptoms or indirectly during routine consultations. The use of screening for asymptomatic fractures is not covered by this guidance.

- 4.3.5 The Committee acknowledged the efforts of the Assessment Group to build on the model used previously, particularly in using the so-far unpublished and complex WHO data to calculate transition probabilities and for modelling the identification approaches. The Committee had previously concluded that the Assessment Group's model was likely to give the best estimates of cost effectiveness because it used data for a wide age range (age 50–80 years), was updated to use all fracture sites and more recent utility, prevalence and risk-factor data, and an adjusted prevalence of fractures in the average population. Although the Assessment Group's model considered a shorter time period (10 years) than the manufacturers' models, the Committee thought that this was appropriate considering the age groups involved and the uncertainties around health effects over a longer period.
- 4.3.6 The Committee considered a recent UK dataset to be the best representation of BMD distribution of women in the UK. The Committee also considered it appropriate to use the BMD, as measured at the femoral neck, to estimate the fracture risk of the hypothetical patient at the threshold of osteoporosis.
- 4.3.7 The Committee considered the extent to which *NICE Technology Appraisal* No. 87 should be updated in the light of new cost effectiveness modelling developed as part of the technology appraisals on primary prevention and strontium ranelate. The new modelling differs from that undertaken for the *NICE Technology Appraisal* No. 87 because it is based on absolute risk of fracture, quantified on the basis of age, T-score and six clinical risk factors using the WHO algorithm. Previous guidance identified those considered to be at risk of fracture using age and T-score only.

Bisphosphonates

- 4.3.8 The Committee considered that there was good evidence to show that, for women with established osteoporosis, alendronate, etidronate and risedronate were all effective in preventing vertebral fractures. Furthermore, alendronate and risedronate reduced the incidence of hip fractures. The

Committee heard from the clinical experts that although an effect of etidronate on non-vertebral fractures is likely, this effect is less pronounced than with alendronate and risedronate, the evidence base is weaker, and the mode of action is slightly different. However, given the lack of direct head-to-head comparisons, the Committee concluded that all of the bisphosphonates under consideration were treatment options for women with established osteoporosis who fulfil the criteria for treatment.

Additionally, the Committee was clear that the choice of bisphosphonate may differ between women and concluded that clinicians and patients need to balance the individual drug's overall proven effectiveness profile against the tolerability and adverse effect profile when deciding which bisphosphonate to prescribe.

4.3.9 The Committee considered the results of the new cost-effectiveness modelling for bisphosphonates in the context of the existing guidance. It was also keen to avoid issuing new guidance which differed from that issued in January 2005 if the evidence base was not significantly different. For bisphosphonates, the Committee concluded that the new modelling led to very similar results to those previously established.

4.3.10 Given the evidence on clinical effectiveness and cost effectiveness, the Committee concluded that bisphosphonates should be recommended as treatment options for women aged 65 years and older who present with an osteoporotic fragility fracture. At the age of 75 years and above, treatment should be started without the need for DXA scanning, because at this age it was considered very likely that women who have sustained a fragility fracture will have a low BMD (T-score of -2.5 SD or below). However, in cases of uncertainty a DXA scan can be performed to confirm osteoporosis. For women between the ages of 65 and 74 years, the Committee considered that alternative causes of fragility fracture should be excluded and therefore treatment is recommended when a T-score of -2.5 SD or below is established by DXA scanning. The Committee felt that, once booked, a long waiting time for a DXA scan need not prevent initiation of

treatment; if appropriate, treatment can be stopped once the result of the DXA scan is available.

- 4.3.11 The Committee considered the clinical experts' views and economic model results concerning women with osteoporotic fragility fractures below the age of 65 years. The Committee noted from the data derived from the WHO study that postmenopausal women younger than 65 years, who had sustained a fracture, were generally at lower risk of further fracture compared with women older than 65 years. However, the economic model indicated that for women aged 50–64 years with an osteoporotic fragility fracture treatment with bisphosphonates was cost effective when these women were considered to be at an increased risk of further fracture. This risk can be recognised as a very low T-score (approximately -3 SD or below). Alternatively, such increased risk can be recognised as confirmed osteoporosis plus one, or more, additional clinical risk factor: parental history of hip fracture; and medical conditions independently associated with bone loss, such as rheumatoid arthritis. The Committee agreed that low body mass index should not be considered as a risk factor because BMD is known.
- 4.3.12 The Committee recognised that women who are unable to comply with the special instructions for the administration of one bisphosphonate may not have such problems with another bisphosphonate. Similarly, women intolerant to one bisphosphonate may tolerate another. Therefore, the Committee considered that the use of another bisphosphonate is appropriate when treatment with a previous bisphosphonate has been discontinued because of inability to comply or intolerance.
- 4.3.13 The Committee further recognised that treatment with bisphosphonates does not confer absolute protection against further fracture, and that the beneficial effect on BMD accrues over many months. It was persuaded that even if a woman sustains a further fracture within the first few months of

bisphosphonate therapy, continuation with bisphosphonate treatment is likely to be the most appropriate therapy in many women.

Strontium ranelate

- 4.3.14 The Committee considered the clinical evidence for strontium ranelate from RCTs and heard statements from experts. It noted that strontium ranelate was effective in preventing vertebral and pooled non-vertebral fractures, and resulted in a non-significant 15% reduction in hip-fracture incidence. The Committee also noted the result of a post-hoc subgroup analysis showing a statistically significant reduction in the incidence of hip fractures in women over the age of 74 and with low BMD. The Committee concluded that the hip-fracture efficacy evidence was less robust for strontium ranelate than for alendronate and risedronate.
- 4.3.15 Strontium ranelate has not previously been appraised and is therefore not included in *NICE Technology Appraisal No. 87*. On the basis of the clinical and cost effectiveness evidence, and after taking the views of the experts into consideration, the Committee concluded that strontium ranelate should be recommended as an alternative treatment option for women in whom bisphosphonates are contraindicated, or who are intolerant of or physically unable to take bisphosphonates, or who have had an unsatisfactory response to bisphosphonates, providing that the age/risk criteria for bisphosphonates are satisfied. The Committee discussed the fact that if hip fracture efficacy data taken from a post-hoc subgroup analysis were used, the cost-effectiveness of strontium ranelate would approximate to that of the bisphosphonates. On balance the Committee did not feel that these data were robust enough to influence their decision.

Raloxifene

- 4.3.16 The Committee considered the evidence from the main RCT showing that raloxifene is effective in preventing vertebral fractures. The clinical experts

acknowledged that there is currently no evidence that raloxifene is effective in preventing non-vertebral fractures.

4.3.17 The Committee discussed the reported benefits of raloxifene on breast cancer risk, and heard from the experts that the possibility of preventing vertebral fractures and breast cancer simultaneously could be attractive to many women. The Committee also heard from the experts that evidence on the effect of raloxifene in reducing cardiovascular risk is not considered to be robust and, furthermore, there is some concern over the risk of VTE.

4.3.18 The Committee noted the overall benefit associated with raloxifene, as observed in the clinical trials in people with osteoporosis. In particular it noted that a higher proportion of this overall benefit was attributable to its effect on the prevention of breast cancer than to its effect on the prevention of osteoporotic fractures. The Committee agreed that, in principle, the side effects of using a technology should be considered, but there were a number of reasons why the Committee considered that the breast cancer benefit should not be the sole factor in deciding whether raloxifene is a cost effective option for the treatment of osteoporosis.

- From the evidence presented, raloxifene was not as effective as bisphosphonates for treating osteoporosis.
- Raloxifene's effect on the prevention of breast cancer has not been assessed by the regulatory authorities.
- Full assessment of raloxifene's effect on the prevention of breast cancer and its cost effectiveness in this indication would require consideration of how it compares with other drugs that potentially could be used for the prevention of breast cancer.

The Committee noted that the cost effectiveness of raloxifene in terms of fracture prevention was very unfavourable relative to the bisphosphonates and strontium ranelate. The existence of strontium ranelate as an option in women for whom bisphosphonates are inappropriate, made the consideration

of raloxifene less relevant than in *NICE Technology Appraisal* No. 87.

However, the Committee concluded that it was not necessary to remove raloxifene as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable to take bisphosphonates and strontium ranelate.

Teriparatide

4.3.19 The Committee considered that evidence from RCTs showed that teriparatide was effective in preventing vertebral and grouped non-vertebral fractures in women with severe osteoporosis, compared with placebo. The Committee also considered the favourable findings for teriparatide from one head-to-head RCT of teriparatide and alendronate, and that it conferred relatively favourable back-pain relief. However, the Committee was concerned about the small size of the head-to-head study, the fact that the study was not targeted at women with fractures, the potential for bias and the higher dose of teriparatide used. Therefore it considered that the evaluation of the overall advantages of teriparatide over bisphosphonates requires more research in order to establish relative clinical and cost effectiveness.

4.3.20 The Committee heard from the clinical experts that they considered two specific situations in which teriparatide was most useful:

- the treatment of particularly severe disease where an effect on stimulation of new bone formation is desirable, rather than just preventing further deterioration of BMD as with the use of anti-resorptive therapy such as bisphosphonates
- where there has been an unsatisfactory response to bisphosphonates.

4.3.21 The Committee considered the results of the new cost-effectiveness modelling in the context of the existing guidance. The Committee considered that the new modelling indicated that there are a small number of women with very low T-scores under the age of 65 who could, if treatment were

contra-indicated for the bisphosphonates and strontium ranelate, be cost-effectively treated with teriparatide. The Committee felt that, given the increased treatment options for such women, on balance, its prior guidance was satisfactory. It agreed that treatment with teriparatide, should be recommended in women aged 65 years and older who are at extremely high risk. This extremely high risk can be recognised through the patient having a T-score of approximately -4 SD (equivalent to an annual absolute fracture risk of at least 5%), or through the patient having a T-score of approximately -3 SD plus multiple fractures (that is, more than two), plus one or more of the following additional risk factors: parental history of hip fracture; untreated premature menopause; conditions associated with prolonged immobility, and ever use of long term-systemic corticosteroids.

Calcium and vitamin D prerequisites for treatment

4.3.22 The Committee discussed the effect of calcium and vitamin D on the clinical effectiveness of the drugs considered. In the studies that formed the basis of this appraisal, all participants were said to have adequate calcium and vitamin D levels. The Committee appreciated that the general population, particularly the elderly, cannot be assumed to have adequate dietary intake of calcium and vitamin D. It was also considered important to note that adequate levels of calcium and vitamin D are needed to ensure optimum effects of the treatments for osteoporosis. The Committee concluded that calcium and/or vitamin D supplementation should be provided unless clinicians are confident that women who receive osteoporosis treatment have an adequate calcium intake and are vitamin D replete.

5 Proposed recommendations for further research

5.1 To enable direct comparisons of efficacy to be made between the different drugs for osteoporosis, the Committee recommends that head-to-head studies should be conducted.

- 5.2 Given the emergence of evidence from one bisphosphonate that the benefits of the drug may continue for several years beyond treatment cessation, the Committee recommends that research should be carried out to define the optimal duration of treatment with individual bisphosphonates.
- 5.3 The Committee recommends research into the long-term effects of bisphosphonates on bone quality, given the inhibitory effects on bone resorption of these drugs.
- 5.4 There is some evidence that strontium ranelate may interfere with the results of DXA scanning as it has similar properties to calcium. It may also affect the measurement of calcium levels in the blood. This could have implications in the clinical care setting and further research is recommended.
- 5.5 The Committee notes that there is an ongoing study to investigate the clinical and cost effectiveness of identifying women at high risk in the prevention of osteoporotic fracture.
- 5.6 The Committee notes that there are ongoing studies investigating the effects of raloxifene on breast cancer and cardiovascular disease risk.

6 Preliminary views on the resource impact for the NHS

The NICE Costing Unit is currently developing this section. A costing template and report will be available at the time of publication of the final guidance.

7 Proposals for implementation and audit

This section presents proposals for implementation and audit based on the preliminary recommendations for guidance in Section 1.

- 7.1 All clinicians in NHS Hospital and Primary Care Trusts who care for postmenopausal women who are at risk of osteoporotic fragility fractures should review their current practice and policies to take account of the guidance set out in Section 1.

- 7.2 Local guidelines, protocols or care pathways that refer to the care of postmenopausal women who are at risk of osteoporotic fragility fractures should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
- 7.3.1 For a woman aged 75 years or older who has had a clinically apparent osteoporotic fracture, bisphosphonates are considered as treatment options without the need for a DXA scan.
- 7.3.2 For a woman aged between 65 and 74 years who has had a clinically apparent osteoporotic fracture, bisphosphonates are considered as treatment options if the presence of osteoporosis is confirmed by DXA scanning.
- 7.3.3 For a postmenopausal woman younger than 65 years of age who has had a clinically apparent osteoporotic fracture, bisphosphonates are considered as treatment options if she has a T-score of approximately -3 SD or below established by a DXA scan or if she has confirmed osteoporosis plus one or more additional clinical risk factors.
- 7.3.4 The woman participates with her clinician in choosing a bisphosphonate. In making the choice, the woman and her clinician consider the drugs' overall proven effectiveness profiles against tolerability and adverse effects.
- 7.3.5 Strontium ranelate is considered as a treatment option for a woman, under the circumstances specified in 7.3.1-7.3.3, if she meets any of the following:
- 7.3.5.1 She has a contraindication to bisphosphonates **or**

- 7.3.5.2 She is unable to comply with the special instructions for the administration of bisphosphonates **or**
 - 7.3.5.3 She has had an unsatisfactory response to bisphosphonates **or**
 - 7.3.5.4 She is intolerant of bisphosphonates.
- 7.3.6 For a woman who is unable to take bisphosphonates, as specified in 7.3.5, raloxifene is considered as a treatment option if she meets one of the following:
- 7.3.6.1 Strontium ranelate is contraindicated **or**
 - 7.3.6.2 She has had an unsatisfactory response to strontium ranelate **or**
 - 7.3.6.3 She is intolerant of strontium ranelate.
- 7.3.7 For a woman aged 65 years or older who has had an unsatisfactory response to bisphosphonates or intolerance to bisphosphonates, teriparatide is considered as a treatment option if she meets one of the following:
- 7.3.7.1 She has an extremely low BMD **or**
 - 7.3.7.2 She has a very low BMD plus multiple fractures plus one or more additional clinical risk factors.
- 7.4 Local clinical audits on the prevention of osteoporotic fragility fractures in postmenopausal women who have sustained a clinically apparent osteoporotic fragility fracture could also include criteria related to the prevention of falls based on the standards in the National Service Framework for Older People or criteria based on the clinical guidelines for prevention and treatment of osteoporosis published by the Royal College of Physicians. Issues that could be addressed in local clinical audits on osteoporosis include

maintaining patient adherence with bisphosphonate drug therapy, educating patients about the condition and treatments, and the involvement of the multiprofessional team in managing patients with osteoporosis.

8 Related guidance

- 8.1 The Institute has issued guidance on technologies for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

National Institute for Clinical Excellence (2005) Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. *NICE Technology Appraisal Guidance No. 87*. London: National Institute for Clinical Excellence.

- 8.2 NICE plans to publish the guidance '*Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women*' in March 2006.
- 8.3 NICE plans to publish the clinical guideline *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk* in June 2006.

9 Proposed date for review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 9.2 It is proposed that the guidance on this technology is considered for review in March 2009.

Andrew Stevens
Chair, Appraisal Committee
September 2005

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets regularly and membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

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Professor of Statistics & Dean Faculty of Natural Sciences, Keele University

Professor Robert Kerwin

Professor of Psychiatry and Clinical Pharmacology, Institute of Psychiatry, London

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner

General Medical Practitioner, Sheffield

Dr Ruairidh Milne

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

Dr Rubin Minhas

General Practitioner, Primary Care Cardiovascular Society

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Dr Ken Stein

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Kate Burslem

Technical Lead, NICE project team

Elisabeth George

Technical Lead, NICE project team

Janet Robertson

Technical Advisor, NICE project team

Cathryn Fuller

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee for the appraisal of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fractures in postmenopausal women

- A The assessment reports for this appraisal was prepared by : The University of Sheffield, School of Health and Related Research (SchARR)

Dr Matt Stevenson, Ms Sarah Davis, Dr Myfanwy Lloyd Jones and Ms Catherine Beverley, *Strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women, July 2005*

Dr Matt Stevenson, Ms Sarah Davis, *Addendum to the Assessment Report: The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women, July 2005*

- B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and assessment report. They are also invited to comment on the Appraisal Consultation Document and consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturers/sponsors:

- Alliance for Better Bone Health
- Eli Lilly & Company Ltd
- Merck Sharp & Dohme Ltd
- Proctor & Gamble Pharmaceuticals
- Servier Ltd

II Professional/specialist and patient/carer groups:

- Arthritis and Musculoskeletal Alliance
- Bone and Tooth Society
- British Geriatrics Society
- British Menopause Society
- British Orthopaedic Association
- British Society for Rheumatology
- Department of Health
- Institute for Ageing and Health
- National Osteoporosis Society
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- RADAR (The Royal Association for Disability and Rehabilitation)

- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Society for Endocrinology
- Southwark Primary Care Trust
- The Society and The College of Radiographers
- Women's Health
- Women's Health Concern
- Women's Nutritional Advisory Service

III Commentator organisations (without the right of appeal):

- British National Formulary
- National Collaborating Centre for Nursing and Supportive Care
- NHS Quality Improvement Scotland
- Novartis Pharmaceuticals Ltd
- Research Institute for the Care of the Elderly
- Strakan Group Ltd
- Welsh Assembly Government

A The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on technologies for the primary prevention of osteoporotic fractures in postmenopausal women by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the Appraisal Consultation Document:

- Mrs Jackie Parrington, Deputy Chief Executive, National Osteoporosis Society – Patient Expert nominated by the National Osteoporosis Society
- Mrs Anthea Franks – Patient Expert nominated by the National Osteoporosis Society
- Professor Juliet Compston, Professor Bone Medicine, Bone and Tooth Society – Clinical Expert nominated by the Royal College of Physicians
- Dr R.M. Francis, Reader in Medicine (Geriatrics) and Honorary Consultant Physician, British Geriatrics Society – Clinical Expert nominated by the British Geriatrics Society and the National Osteoporosis Society
- Dr Caje Moniz, Consultant and Clinical Director, King's Healthcare NHS Trust – Clinical Expert nominated by the National Osteoporosis Society
- Dr Peter Selby, Consultant Physician, Central Manchester and Manchester Children's University Hospitals NHS Trust – Clinical Expert nominated by the Society of Endocrinology and the National Osteoporosis Society

Appendix C. Detail on criteria for audit of the use of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fractures in postmenopausal women

Possible objectives for an audit

An audit could be carried out to ensure the appropriateness of the consideration of technologies, specifically bisphosphonates (alendronate, etidronate, risedronate), raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

Possible patients to be included in the audit

An audit could include all women who have sustained a clinically apparent osteoporotic fracture in a reasonable time period for audit, for example, all those who are seen in a general practice or who are treated in a hospital in 6 months. Postmenopausal women with corticosteroid-induced osteoporosis should be excluded from this audit.

The audit measures below assume that the women in the audit have normal levels of calcium and/or vitamin D. If women are included in the audit who do not have normal calcium levels and/or vitamin D levels, measures related to calcium and/or vitamin D supplements should be added.

Measures that could be used as a basis for an audit

The measures that could be used in an audit on the appropriate consideration of prescribing bisphosphonates, raloxifene, strontium ranelate and teriparatide are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. For a woman aged 75 years or older who has had a clinically apparent osteoporotic fracture, bisphosphonates are considered as treatment options without the need for a DXA scan</p>	<p>100% of women aged 75 years and older who have had a clinically apparent osteoporotic fracture</p>	<p>A. The woman has a contraindication to bisphosphonates B. The woman is unable to comply with the special instructions for the administration of bisphosphonates C. The woman has had an unsatisfactory response to bisphosphonates D. The woman is intolerant of bisphosphonates E. The woman declines treatment after discussion with her clinician (see 4 below)</p>	<p>Bisphosphonates are alendronate, etidronate or risedronate. See Summaries of Product Characteristics for a description of contraindications for bisphosphonates and special recommendations for use of bisphosphonates. 'An unsatisfactory response to bisphosphonates' occurs when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is also evidence of a decline in BMD below her pre-treatment baseline. 'Intolerance of bisphosphonates' is defined as oesophageal ulceration, erosion or stricture, any of which warrants discontinuation of treatment with a bisphosphonate. Clinicians will need to agree locally on how a clinically apparent osteoporotic fracture and consideration of treatment options are documented for audit purposes.</p>

<p>2. For a woman aged between 65 and 74 years who has had a clinically apparent osteoporotic fracture, bisphosphonates are considered as treatment options if the presence of osteoporosis is confirmed by DXA scanning</p>	<p>100% of women aged between 65 and 74 years who have had a clinically apparent osteoporotic fracture and DXA confirmed osteoporosis</p>	<p>A. The woman has a contraindication to bisphosphonates B. The woman is unable to comply with the special instructions for the administration of bisphosphonates C. The woman has had an unsatisfactory response to bisphosphonates D. The woman is intolerant of bisphosphonates E. The woman declines treatment after discussion with her clinician (see 4 below)</p>	<p>See above for relevant definitions. 'DXA confirmed osteoporosis' means a T-score of -2.5 or below.</p>
<p>3. For a postmenopausal woman younger than 65 years of age who has had a clinically apparent osteoporotic fracture, bisphosphonates are considered as treatment options if she has one of the following:</p> <p>a. a T-score of approximately -3 SD or below established by a DXA scan or</p> <p>b. confirmed osteoporosis plus one or more additional clinical risk factors</p>	<p>100% of women aged younger than 65 years who have had a clinically apparent osteoporotic fracture and who meet 3a or 3b</p>	<p>A. The woman has a contraindication to bisphosphonates B. The woman is unable to comply with the special instructions for the administration of bisphosphonates C. The woman has had an unsatisfactory response to bisphosphonates D. The woman is intolerant of bisphosphonates E. The woman declines treatment after discussion with her clinician (see 4 below)</p>	<p>See above for relevant definitions. 'Clinical risk factors' are parental history of hip fracture; and medical conditions independently associated with bone loss such as rheumatoid arthritis.</p>
<p>4. The woman participates with</p>	<p>100% of women who have had a</p>	<p>A. The woman declines</p>	<p>Clinicians will need to agree locally on</p>

<p>her clinician in choosing a bisphosphonate</p>	<p>clinically apparent osteoporotic fracture and for whom bisphosphonates are being considered as treatment options and who do not meet Exceptions</p>	<p>participating in discussion about the options with her clinician</p>	<p>how discussion between the woman and the clinician is documented for audit purposes. The discussion should reflect consideration of the drugs' overall proven effectiveness profiles, tolerability and adverse effects.</p>
<p>5. Strontium ranelate is considered as a treatment option for a woman who has had a clinically apparent osteoporotic fracture, if she meets the circumstances in 1, 2 or 3 above and any of the following:</p> <ul style="list-style-type: none"> a. She has a contraindication to bisphosphonates or b. She is unable to comply with the special instructions for the administration of bisphosphonates or c. She has had an unsatisfactory response to bisphosphonates or d. She is intolerant of bisphosphonates 	<p>100% of women who have had a clinically apparent osteoporotic fracture and who meet any of 1, 2 or 3 and any of 5a–d</p>	<p>A. The woman has a contraindication to strontium ranelate</p>	<p>See above for relevant definitions. See Summary of Product Characteristics for contraindications to strontium ranelate.</p>
<p>6. For a woman who is unable to take bisphosphonates, raloxifene is considered as a treatment option if</p>	<p>100% of women who have had a clinically apparent osteoporotic fracture, who are unable to take</p>	<p>None</p>	<p>See above for relevant definitions. 'Unable to take bisphosphonates' is defined in 5a–d. 'Intolerance of</p>

<p>she meets one of the following:</p> <p>a. Strontium ranelate is contraindicated or</p> <p>b. She has had an unsatisfactory response to strontium ranelate or</p> <p>c. She is intolerant of strontium ranelate</p>	<p>bisphosphonates and who meet 6a or 6b or 6c</p>		<p>strontium ranelate' is defined as persistent nausea or diarrhoea, either of which warrants discontinuation of treatment with strontium ranelate.</p>
<p>7. For a woman aged 65 years or older who has had an unsatisfactory response to bisphosphonates or intolerance to bisphosphonates, teriparatide is considered as a treatment option if she meets one of the following:</p> <p>a. She has an extremely low BMD or</p> <p>b. She has a very low BMD plus multiple fractures plus one or more additional clinical risk factors</p>	<p>100% of women aged 65 years or older who have had an unsatisfactory response or intolerance to bisphosphonates and who meet 7a or 7b</p>	<p>None</p>	<p>See above for relevant definitions. 'Extremely low BMD' means a T-score of -4 SD or below. 'Very low BMD' means a T-score of approximately -3 SD or below. 'Multiple fractures' means more than 2.</p>

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **excep**tion listed}}{\text{Number of patients to whom the **meas**ure applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.