NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

1 Guidance

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 calcium levels and/or vitamin D levels. 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.

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 prior dual energy X-ray absorptiometry (DEXA) scanning
- in women aged between 65 and 75 years if the presence of osteoporosis is confirmed by DEXA scanning, and
• in postmenopausal women younger than 65 years of age, if they have a very low bone mineral density (BMD, that is with a T-score of approximately –3 SD or below\(^*\), established by a DEXA scan), or if they have confirmed osteoporosis plus one, or more, additional age-independent risk factor: low body mass index (< 19 kg/m\(^2\)); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; certain medical disorders independently associated with bone loss (such as chronic inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism or coeliac disease); conditions associated with prolonged immobility.

1.2 In their choice of bisphosphonate, clinicians and patients need to balance the drug’s overall proven effectiveness profile against tolerability and adverse effects in individual patients.

1.3 Raloxifene 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 physically unable to comply with the special recommendations for use of bisphosphonates, or
- who have had an unsatisfactory response to bisphosphonates (as defined in Section 1.5), or
- who are intolerant of bisphosphonates (as defined in Section 1.6).

1.4 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 (as defined in Section 1.5) and:

\(^*\) For T-score definition, see Sections 2.3 and 2.4
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 age-independent risk factor: low body mass index (< 19 kg/m²); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; conditions associated with prolonged immobility.

1.5 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.

1.6 For the purpose of this guidance, intolerance of bisphosphonates is defined as oesophageal ulceration, erosion or stricture, or lower gastrointestinal symptoms, any of which warrants discontinuation of treatment with a bisphosphonate.

2 Clinical need and practice

2.1 Osteoporosis is defined as 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 between the third and fifth decade of life there is a gradual loss of bone mass. Therefore, age is one of the major risk factors for primary osteoporosis. It can affect both sexes, but postmenopausal women are at the greatest risk, because bone loss is accelerated, to varying degrees, after the menopause because of loss of oestrogen production.
2.3 The World Health Organization (WHO) classification of osteoporosis has been widely adopted and is based on the measurement of BMD, with reference to the number of SDs from the BMD in an average 25-year-old woman (T-score):

- normal: T-score of –1 SD or more
- osteopenia: T-score between –1 and –2.5 SD
- osteoporosis: T-score below –2.5 SD
- established osteoporosis: T-score below –2.5 SD, with one or more associated fragility fractures.

2.4 BMD T-scores can vary by site and method of measurement. Reference standards have been published for the different measurement sites. The prediction of fracture risk is usually based on BMD measurements at the femoral neck.

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 1.2 million. Prevalence increases markedly with age after the menopause, and approximately 30% of women in England and Wales aged 80 years and older are estimated to have osteoporosis. The annual incidence of symptomatic osteoporotic fractures (including recurrent fractures) is approximately 180,000 (see Section 2.8). However, many vertebral fractures may not come to clinical attention.

2.6 Risk factors for osteoporosis include low body mass index (< 19 kg/m²), untreated premature menopause, family history of maternal hip fracture before the age of 75 years, conditions affecting bone metabolism (primarily inflammatory conditions, hyperthyroidism or coeliac disease), and conditions associated with prolonged immobility. Osteoporosis is most common in white women. The quantitative impact of these individual risk factors on the
absolute risk of a primary or secondary osteoporotic fracture is currently being established by the WHO.

2.7 People with osteoporosis are at risk of fragility fractures. These are fractures that occur as a result of mechanical forces that would not ordinarily cause fracture. The WHO has quantified this as forces equivalent to a fall from a standing height or less. Osteoporotic fragility fractures occur most commonly in the vertebrae, hips and wrists, and are frequently associated with substantial disability, pain and reduced quality of life. In the absence of fracture, the condition is asymptomatic and often remains undiagnosed.

2.8 The incidence of fragility fracture is the clinically relevant outcome in evaluating treatments for osteoporosis. Of the estimated 180,000 symptomatic osteoporotic fractures annually in England and Wales, 70,000 are hip fractures, 25,000 are vertebral fractures, and 41,000 are wrist fractures. In 2000, it was estimated that the total cost of treating osteoporotic fractures in postmenopausal women was between £1.5 and £1.8 billion. This is expected to increase to £2.1 billion by 2010.

2.9 In women older than 50 years of age, the lifetime risk of vertebral fracture is estimated to be about one in three (including asymptomatic vertebral fractures), and approximately one in six for hip fracture. Postmenopausal women with an initial fracture are at much greater risk of subsequent fractures.

2.10 After treatment for hip fracture, many women are unable to walk independently or perform other activities of daily living and so are unable to continue to live independently. Hip fractures are also associated with increased mortality. In the 12 months after hip fracture, estimates of the relative mortality risk vary from two to more than ten, depending on age. However, it is unclear to what extent this can be independently attributed to fracture.
2.11 For the treatment of osteoporosis, the Royal College of Physicians’ guidelines on the treatment of osteoporosis and the National Service Framework for Older People recommend a selective case-finding approach, the use of BMD measurement, and drug treatment focused on women with fractures or multiple risk factors.

2.12 A number of interventions are used to preserve bone mass and prevent fracture. Lifestyle modifications include regular weight-bearing exercise, avoidance of smoking, and moderation of alcohol intake. In older patients, fall prevention measures, such as home modifications, and hip protectors may also be considered. Drug therapies and supplements include hormone replacement therapy (HRT), bisphosphonates, selective oestrogen receptor modulators (SERMs), parathyroid hormone, calcitonin, calcium, vitamin D, and calcitriol. It has been estimated that in the UK 10–20% of women with osteoporosis receive drug treatment for the condition. The choice of interventions is influenced by factors such as BMD, stage of disease progression, nature and site of fracture, patient age, underlying co-morbidities and side effects.

3 The technologies

Bisphosphonates: alendronate, etidronate, risedronate

3.1 Bisphosphonates are inhibitors of bone resorption and increase BMD by altering both osteoclast activation and function. Three bisphosphonates, alendronate, etidronate and risedronate, are currently licensed in the UK for the management of osteoporosis. It has been estimated that approximately 275,000 women in England and Wales are prescribed bisphosphonates.

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 also £23.12 for four 70-mg tablets.
(excluding VAT; *British National Formulary* [BNF] 47th edition). This equates in each case to between £0.83 per day of treatment. Costs may vary in different settings because of negotiated procurement discounts. In 2003/04, 61% of prescriptions for bisphosphonates in England were for alendronate.

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 £40.20 (excluding VAT; *BNF* 47th edition), which equates to £0.45 per day of treatment. Costs may vary in different settings because of negotiated procurement discounts. In 2003/04, 23% of prescriptions for bisphosphonates in England were for etidronate.

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 £21.83 for 28 5-mg tablets and also £21.83 for four 35-mg tablets (excluding VAT; *BNF* 47th edition), which equates, in each case to £0.78 per day of treatment. Costs may vary in different settings because of negotiated procurement discounts. In 2003/04, 16% of prescriptions for bisphosphonates in England were for risedronate.

3.5 The use of bisphosphonates is contraindicated in people with hypocalcaemia. The use of risedronate and etidronate is contraindicated in people with severe renal impairment. For full details of side effects and contraindications, see the Summaries of Product Characteristics.

3.6 Bisphosphonates should be used cautiously when they are given to patients with active upper gastrointestinal problems. The bisphosphonates have complex modes of 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 £21.74 and £65.21, respectively (excluding VAT; *BNF*, 47th edition), which equates to £0.78 per day of treatment. Costs may vary in different settings because of negotiated procurement discounts. In 2003/04, 6% of the combined prescriptions of bisphosphonates and raloxifene in England were for raloxifene.

3.9 Particular contraindications include 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 also 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 HRT. For full details of side effects and contraindications, see the Summary of Product Characteristics.
Parathyroid hormone: teriparatide

3.10 Teriparatide (Eli Lilly and Company Ltd) is a recombinant human parathyroid hormone and, as an anabolic agent, it stimulates new formation of bone. It is also claimed to increase resistance to fracture.

3.11 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, 47th edition), which is equal to £9.71 per day of treatment. Costs may vary in different settings because of negotiated procurement discounts.

3.12 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 (see Appendix A) considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Report reviewed data from 39 published randomised controlled trials (RCTs) in postmenopausal women where fracture or health-related quality of life was a primary endpoint and where one of the five drugs of interest was compared with a relevant comparator including: no treatment, placebo, calcium, vitamin D derivatives, or HRT. 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 of interventions for the secondary prevention of osteoporotic fractures, principally data related to women with established osteoporosis was considered.

4.1.3 For vertebral fractures, some studies used clinical (that is, symptomatic) fractures as their endpoint whilst 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 grouped data on non-vertebral fractures.

4.1.5 Alendronate

4.1.5.1 Sixteen RCTs of alendronate in postmenopausal women were reviewed 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 A 2-year RCT demonstrated the equivalence of weekly and daily doses of alendronate, in terms of clinical fracture incidence and upper-gastrointestinal (GI) adverse events.

4.1.5.4 The largest study of alendronate, the Fracture Intervention Trial (FIT), comprised two placebo-controlled sub-studies in different populations: one in women with pre-existing fractures (established osteoporosis, \( n = 1946 \)) and another in women without pre-existing fractures (\( n = 4134 \)). The sub-study in women with established osteoporosis found a relative risk (RR) of vertebral fracture of 0.53 (95% confidence interval [CI] 0.41 to 0.68), an RR of hip fracture of 0.49 (95% CI, 0.24 to 1.01) and an RR of wrist fracture of 0.52 (95% CI, 0.33 to 0.92) for alendronate relative to placebo.

4.1.5.5 Adverse upper-GI events including nausea, dyspepsia, mild oesophagitis/gastritis and abdominal pain were reported in about 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 upper-GI 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.

4.1.6 Etidronate

4.1.6.1 Eleven 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; and five in women with established osteoporosis. Four of these included active comparators, and seven 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 For vertebral fractures in women with established osteoporosis, a pooled analysis of two studies using a 20% reduction in vertebral height as the fracture definition and cyclical etidronate at a dose of 400 mg/day, found an RR of 0.43 (95% CI, 0.20 to 0.91) in favour of those treated with etidronate compared with untreated controls.

4.1.6.3 For the prevention of non-vertebral fractures, there was no statistically significant evidence from RCTs that etidronate is effective. An analysis of pooled data from four studies found an RR of 1.04 compared with controls in women with established osteoporosis (95% CI, 0.64 to 1.69). Only one of these studies provided separate information on hip fractures (RR 0.50; 95% CI, 0.05 to 5.34) but with insufficient power to show a statistically significant difference.

4.1.6.4 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 a relative risk of non-vertebral fracture of 0.80 (95% CI, 0.70 to 0.92). The relative 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).

4.1.6.5 Higher rates of upper-GI 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 upper-GI 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 A pooled analysis of two studies in women with established osteoporosis, using the licensed UK dose (5 mg/day) and a 15% reduction in vertebral height as the vertebral fracture definition, found an RR of vertebral fracture of 0.63 (95% CI, 0.51 to 0.78) compared with placebo, and an RR of non-vertebral fracture of 0.67 (95% CI, 0.50 to 0.90).

4.1.7.3 For hip/pelvis fractures, a pooled analysis of two studies comparing risedronate with placebo in women with established osteoporosis failed to show a statistically significant protective treatment effect (RR 0.77; 95% CI, 0.46 to 1.27). However, with the addition of unpublished data from a third study of women aged 70–79 years with established osteoporosis, a statistically significant protective effect on hip fracture was found (RR 0.60; 95% CI, 0.42 to 0.88). This additional data included women receiving 2.5- and 5-mg doses of risedronate – a difference that did not affect the level of protection against hip fracture among the women in this age group, according to the author’s calculations.

4.1.7.4 The two studies that provided data on wrist and humerus fractures in women with established osteoporosis were insufficiently powered to show
whether risedronate has a beneficial effect (RR 0.68; 95% CI, 0.43 to 1.08). However, pooled data from these studies found a statistically significant effect on fracture of the humerus (RR 0.46; 95% CI 0.73 to 0.93).

4.1.7.5 Overall and upper-GI adverse events were similar in the risedronate and placebo groups in all of the studies.

4.1.8 Raloxifene

4.1.8.1 Two RCTs of raloxifene in postmenopausal women were identified: one in women with osteoporosis, of whom 37% had vertebral fracture at entry, the other 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. One study – the Multiple Outcomes of Raloxifene Evaluation (MORE) study – was extended to further assess fracture, breast cancer, and cardiovascular and uterine safety outcomes.

4.1.8.2 For vertebral fracture, defined as a 20% reduction in vertebral height, the MORE study found a RR, in women with osteoporosis or established osteoporosis, of 0.65 (95% CI, 0.53 to 0.79) at 60 mg, and of 0.54 (95% CI, 0.44 to 0.67) at 120 mg, in favour of raloxifene compared with placebo. The RR in women with established osteoporosis, 0.69 (95% CI, 0.56 to 0.86) at 60 mg and 0.51 (95% CI, 0.40 to 0.65) at 120 mg. The smaller study of women with established osteoporosis failed to find a statistically significant difference in vertebral fractures, using a 15% height reduction definition. A re-analysis, using a definition of 30% reduction or more, found a statistically significant reduction in risk in the 120-mg group only (RR 0.31; 95% CI, 0.11 to 0.87).
4.1.8.3 For hip and wrist fractures and grouped non-vertebral fractures, the evidence did not demonstrate that raloxifene has a preventative effect. The MORE study, which included women with and without previous fracture, examined pooled non-vertebral fractures, but no statistically significant differences between raloxifene and placebo were found (RR 0.92; 95% CI, 0.79 to 1.07). However, it may be that the ability of the MORE study to detect such differences was undermined by loss of women from the study, particularly in the control group, because of disease progression.

4.1.8.4 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 have also been found with raloxifene compared with placebo.

4.1.8.5 The MORE study suggests that raloxifene may protect 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 Teriparatide

4.1.9.1 Three RCTs of teriparatide in postmenopausal women were considered: one study compared teriparatide with alendronate in women with osteoporosis (but 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 HRT for at least 2 years.
4.1.9.2 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.

4.1.9.3 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.

4.1.9.4 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).

4.1.9.5 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.

4.1.9.6 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

4.2.1 The Assessment Group provided a cost–utility model based on a modified, individualised Markov approach. The cost effectiveness was estimated separately for women at different ages (50, 60, 70 and 80 years), who have a T-score of –2.5 SD and who have had a fragility fracture; this was the baseline risk in the modelling. As fracture risk can be increased by a further decrease in BMD or by other clinical risk factors as described in section 2.6, the Assessment Group also nominally increased the baseline risk by factors of 2 and 4 (respectively called ‘doubled risk’ and ‘quadrupled risk’ below).

4.2.2 The prevalence of fractures for women with a Z-difference of 0 was calculated and adjusted for different T-scores. For every age-cohort, the Z-difference was calculated as the difference between the T-score of the hypothetical patient (T-score of –2.5 SD) and the average T-score of the age-cohort. The Assessment Group model was based on BMD data from the UK, and calculated fracture risk based on femoral neck T-scores. The model simulated patients either until they died or for up to 10 years (5 years of treatment plus 5 years linear fall time [that is, decline of effect to zero], except for teriparatide, where the fall time was 1 year). Although the time horizon was 10 years, the additional utility gained, through mortality prevented, was taken into consideration using a life-table approach. The comparator for the analyses was no treatment, but an adequate intake of calcium and vitamin D was assumed for all patients.
4.2.3 The cost–utility model included three additional variables to determine an appropriate cost per QALY for all technologies under appraisal: an age-dependent gradient of hip fracture risk by Z-difference, the introduction of mortality related to vertebral and proximal humerus fractures, and an increase in the disutility associated with proximal humerus fractures.

4.2.4 Alendronate

4.2.4.1 Generally, the cost per quality-adjusted life-year gained (CQG) improved with increasing patient age after the age of 60. Using the Assessment Group’s model for women with a T-score of –2.5 SD, the CQG ranged from £32,937 (age 50), and £36,595 (age 60), to £12,191 (age 70) and to dominating (that is, cost saving) at age 80. For women with doubled risk, the CQG was £15,149 or less for all age groups.

4.2.4.2 The manufacturer provided a CQG for alendronate, derived from its own model, of £3135 for 70-year-old women with a T-score below –1.6 SD.

4.2.4.3 The manufacturer’s model gave more favourable CQG values than did 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.

4.2.5 Etidronate

4.2.5.1 Using the Assessment Group’s model and the assumption that etidronate only affects vertebral fractures, the CQG for women with a T-score of -2.5 SD ranged from £84,996 (age 50), and £91,334 (age 60), to £27,551 (age 70) and £39,315 (age 80). For women with doubled risk, the CQG ranged from £41,382 (age 50), and £44,601 (age 60), to £12,216 (age 70) and £15,683 (age 80).
4.2.5.2 When observational data on hip and wrist fractures were included in the transition probabilities, the CQG for women with a T-score of –2.5 SD, ranged from £242,345 (age 50), and £46,717 (age 60), to £14,517 (age 70) and £6687 (age 80). For women with doubled risk, the CQG was £21,154 or less for all age groups.

4.2.5.3 The manufacturer’s model included morphometric vertebral fractures and corticosteroid use as risk factors for further fractures, and resulted in a CQG of £18,634 for age 70 and an approximately three-fold risk. It is unclear whether the manufacturer’s CQG figure was for women with or without osteoporotic fragility fracture.

4.2.6 Risedronate

4.2.6.1 The CQG improved with increasing patient age after the age of 60. Using the Assessment Group’s model for women with a T-score of –2.5 SD the CQG ranged from £37,030 (age 50), and £38,645 (age 60), to £15,067 (age 70) and dominating (age 80). For women with doubled risk, the CQG was £16,406 or less for all age groups.

4.2.6.2 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 (age 60) to £4800 (age 80) for women with an osteoporotic fragility fracture (specified as vertebral) and a T-score of –2.5 SD. For women at slightly higher risk, the corresponding CQGs were £18,600 or less for all age groups.

4.2.6.3 The CQG figure provided by the manufacturer’s own model is difficult to substantiate from the information given. The CQG figures provided by the second model are in reasonable agreement with the figures provided by the Assessment Group’s model.
4.2.7 Raloxifene

4.2.7.1 In addition to the economic analyses carried out by the Assessment Group and the manufacturer, the NICE Decision Support Unit (DSU) conducted further economic analyses. There was no evidence that raloxifene has an effect on hip or wrist fractures and therefore only the effect on vertebral sites was included in the modelling of fractures. Because raloxifene may have beneficial side effects, additional model inputs in some of the analyses included the risks of contracting breast cancer and of dying because of breast cancer.

4.2.7.2 When the breast cancer benefit was not included, the CQG data were more than £72,000 for all age groups with no additional risk factors. Raloxifene treatment of women aged 70 and 80 in the doubled risk group gave CQGs of £34,737 and £49,941, respectively.

4.2.7.3 For the modelling of the breast cancer benefit in the DSU model, the Adjuvant Breast Cancer group model was adapted and updated, and for raloxifene, the probability of breast cancer was based on the RR of 0.38 (95% CI, 0.24 to 0.58) from the MORE study. Including the breast cancer benefit led to CQGs of £30,659 or less for women with a T-score of -2.5 SD, except at the age of 80 when the CQG was £56,048.

4.2.7.4 The manufacturer provided a CQG for raloxifene for different age groups and different risk levels, but it was not clear how different risk levels were defined. The CQG figures varied from £12,000 to £22,000.

4.2.7.5 The manufacturer’s model resulted in more favourable CQG figures than the Assessment Group and DSU models. 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. The RR for the breast cancer effect was lower in the manufacturer’s model (0.28 for invasive breast cancer) than in the
Assessment Group and DSU models. In the Assessment Group and DSU models, the breast cancer risk was adjusted for the association between low BMD and decreased risk of breast cancer.

4.2.7.6 The costs and benefits associated with the effect on cardiovascular disease (CVD) events were also estimated using an adapted model of a previously published CVD model. This reduced the CQG by approximately 8–17%. However, the authors of the DSU advise against the inclusion of the CVD effects, because the MORE study did not report data on the CVD baseline risk profile of the study groups, and used a relatively crude risk-scoring system in the analysis of CVD benefits. Also, the MORE study did not report age-specific CVD event rates.

4.2.7.7 A potentially serious adverse event associated with raloxifene in the MORE study was an increase in thromboembolic disease (RR 2.35; 95% CI, 1.20 to 4.62; for 60 mg raloxifene). Based entirely on the number of cases observed within the study, the DSU report estimated that an additional 0.63 cases of thromboembolic disease would be expected in a population of 100 women.

4.2.8 Teriparatide

4.2.8.1 The economic analyses for teriparatide were carried out using hypothetical populations at high risk of fracture. The manufacturer’s model uses an approximately quadrupled risk of fracture compared with the average population and the Assessment Group’s model included data for doubled and quadrupled risk compared with baseline risk. Both analyses assumed that the comparator was no treatment.

4.2.8.2 Using the Assessment Group’s model the CQG improved with increasing patient age after the age of 60. For doubled risk, the CQG ranged from £91,657 at age 50 and £102,418 at age 60, to £43,827 at age 70 and £30,687 at age 80. For quadrupled risk, the CQG ranged from £43,968 at age 50, and £48,443 at age 60, to £18,266 at age 70 and £7371 at age 80.
4.2.8.3 The manufacturer provided CQGs for teriparatide for women aged 69 years. For women with fractures 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.

4.2.8.4 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.

4.2.8.5 Another major difference between the models concerned the effect of teriparatide on hip fracture and other non-vertebral fractures, which is still uncertain. A separate analysis was run in the Assessment Group’s model assuming no effect at the hip, wrist or proximal humerus, resulting in CQGs that range from £42,474 at age 70 to £133,203 at age 60. When hip fracture effects and other non-vertebral fractures were included the Assessment Group’s model incorporated the wide confidence interval around the RR (95% CI, 0.09 to 2.73), whereas the manufacturer’s model considered only the mean RR for hip fracture.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of bisphosphonates (alendronate, etidronate and risedronate), SERMs (raloxifene) and parathyroid hormone (teriparatide), having considered evidence on the nature of the condition and the value placed on the benefits of the drugs by people with osteoporosis, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took 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 age-independent risk factors, such as low body mass index (< 19 kg/m²), family history of maternal hip fracture before the age of 75 years, untreated premature menopause, certain medical disorders independently associated with bone loss, such as chronic inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism or coeliac disease, and conditions associated with prolonged immobility. The Committee was also mindful that long-term corticosteroid use, as a principal risk factor, requires separate consideration and is not covered in this guidance.

4.3.3 Although the Committee acknowledged that BMD and age are not the sole determinants for predicting future fracture risk, they are key risk factors and are currently the only quantifiable determinants. The Committee was advised by the experts that the impact and strength of other risk factors is currently difficult to estimate. Therefore, the Committee relied predominantly on BMD and age in the estimation of risk and therefore of cost effectiveness. The Committee recognised the need to include other risk factors in a quantifiable way, and suggested that this guidance should be reviewed as soon as a reliable method of aggregating different risk factors is available, for example, the risk algorithm currently being developed by the World Health Organization.

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 for other purposes. This guidance specifically applies to women who present with clinically apparent fractures identified directly by symptoms or indirectly during routine consultations for other purposes. The use of screening for asymptomatic fractures is not covered by this guidance.
4.3.5 The Committee 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), 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 time span.

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.

Bisphosphonates

4.3.7 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 were treatment options for women with established osteoporosis who fulfil the criteria for treatment. Additionally, the Committee were clear that the choice of bisphosphonate may differ between patients 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.
4.3.8 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 DEXA 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 DEXA scan can be performed to confirm osteoporosis. For women between the ages of 65 and 75 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 DEXA scanning. The Committee felt that, once booked, a long waiting time for a DEXA scan need not prevent initiation of treatment; if appropriate, treatment can be stopped once the result of the DEXA scan is available.

4.3.9 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 concluded 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 (nominally doubled compared with women with a previous fracture and a T-score of –2.5 SD). In terms of BMD, 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 age-independent risk factor: low body mass index (< 19 kg/m²); family history of maternal hip fracture before age 75; untreated premature menopause; conditions affecting bone
metabolism (primarily inflammatory conditions, hyperthyroidism or coeliac disease); conditions associated with prolonged immobility.

4.3.10 The Committee recognised that women who are unable to comply with the special recommendations for the use 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.

4.3.11 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. They were 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.

Raloxifene

4.3.12 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.

4.3.13 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 venous thromboembolism.
4.3.14 The Committee noted the overall benefit associated with raloxifene, as observed in the clinical trials in people with osteoporosis. In particular they noted the higher proportion of this overall benefit 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.
- The long-term risks of raloxifene treatment are uncertain.
- 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.

4.3.15 On the basis of the above considerations the Committee concluded that raloxifene should be recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women in whom bisphosphonates are contraindicated, or who are physically unable to take bisphosphonates, or who have had an unsatisfactory response to, or are intolerant of bisphosphonates, using otherwise the same age and risk criteria as defined for bisphosphonates.

Teriparatide

4.3.16 The Committee considered that evidence from RCTs showed that teriparatide was effective in preventing vertebral and 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 and therefore they considered that the evaluation of the overall advantages of teriparatide over bisphosphonates requires more research in order to establish relative clinical and cost effectiveness.

4.3.17 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.

4.3.18 The Committee considered the results of the economic model which showed that treatment with teriparatide, when compared with no treatment, is cost effective for women aged 65 years and older who are at extremely high risk (nominally a four-fold higher risk than for women with a fragility fracture and T-score of –2.5 SD). Because of the difficulty in quantifying risk, the Committee agreed that until a risk algorithm becomes available, this extremely high risk can be recognised through the patient having a T-score of approximately –4 SD, 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: low body mass index (< 19 kg/m²); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; conditions associated with prolonged immobility.
Calcium and vitamin D prerequisites for treatment

4.3.19 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 Recommendations for further research

5.1 The Institute recommends that an algorithm aggregating different risk factors for the prediction of risk for osteoporotic fragility fracture in individual patients should be developed.

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

5.3 Given the emergence of evidence from one bisphosphonate that the benefits of the drug may continue for several years beyond treatment cessation, the Institute recommends that research should be carried out to define both the optimal duration of treatment with individual bisphosphonates, and the most beneficial age at which to start treatment.

5.4 The Institute recommends that research should be conducted to determine the efficacy of teriparatide in preventing fractures in postmenopausal women.
with osteoporosis who have had an inadequate clinical response to bisphosphonates.

5.5 The Institute notes that there are ongoing studies investigating the effects of raloxifene on breast cancer and cardiovascular disease risk.

6 Implications for the NHS

6.1 Prescribing data for England from 2003/04 indicate that £66 million was spent on alendronate, £16 million on risedronate, £13.7 million on etidronate and £6.9 million on raloxifene. In the first 3 months of 2004, £7341 was spent on teriparatide.

6.2 It is possible that the guidance could increase use of bisphosphonates in women with osteoporotic fragility fractures and increase the use of DEXA scans in younger women. However, because information on current prescribing, in terms of age and fracture status is not available, it is not possible to provide precise data on the overall impact of this guidance on NHS prescribing costs.

6.3 It has been estimated that, in England and Wales, there are around 180,000 symptomatic osteoporotic fractures per year. Based on population statistics and the simplifying assumption that all of these fractures occur in postmenopausal women, it can be estimated that approximately 50% of these fractures occur in women over the age of 75 years, and 25% each in women aged 65–74 years and 50–64 years. If the proportion of women with new osteoporotic fractures who are treated with bisphosphonates was 100% in the age group over 75 years, 60% in the age group 65–74 years and 20% in the age group 50–64 years, the cost to the NHS in England and Wales of providing secondary prevention treatment for these women would be around £33 million in the first year. Treatment can be assumed to continue for more than one year; therefore this estimated cost would increase annually. However, because of lack of information on actual treatment duration it is not possible to predict when a steady state of cost would be reached.
 Appropriately directed treatment could also result in cost savings through avoided fractures.

6.4 As it is not known how many women are intolerant of, or do not have a satisfactory response to bisphosphonates, it is not possible to predict the cost for raloxifene. Teriparatide is recommended for a very small proportion of the patient group (women who are both at very high risk of fracture, and who have failed to respond satisfactorily to treatment with bisphosphonates). It is not possible to estimate the exact number of women in this group. However, if 1000 women per year received treatment with teriparatide, the cost would be approximately £3.5 million per year, and the treatment would be continued for 1.5 years.

6.5 It is likely that the guidance could increase the demand for DEXA scanning and may therefore necessitate an increase in DEXA capacity.

7 Implementation and audit

7.1 All clinicians in NHS Hospital and Primary Care Trusts who care for postmenopausal women who have had an osteoporotic fragility fracture 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 have had an osteoporotic fragility fracture 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 an osteoporotic fragility fracture, bisphosphonates are considered as treatment options for the secondary prevention of an osteoporotic fragility fracture, without the need for DEXA scanning.
7.3.2 For a woman aged between 65 and 75 years old who has had an osteoporotic fragility fracture, bisphosphonates are considered as treatment options for the secondary prevention of an osteoporotic fragility fracture, with DEXA-confirmed osteoporosis.

7.3.3 For a postmenopausal woman younger than 65 years of age who has had an osteoporotic fragility fracture, bisphosphonates are considered as treatment options if the woman has a very low bone mineral density or confirmed osteoporosis plus one or more additional age-independent risk factors.

7.3.4 For a postmenopausal woman with osteoporosis who has had an osteoporotic fragility fracture, raloxifene is considered as an alternative treatment option, under the circumstances specified in Sections 7.3.1 to 7.3.3 if she meets any of the following.

- She has a contraindication to bisphosphonates.
- She is physically unable to comply with the special recommendations for use of bisphosphonates.
- She has had an unsatisfactory response to bisphosphonates.
- She is intolerant of bisphosphonates.

7.3.5 For a woman aged 65 years or older who has had an unsatisfactory response to bisphosphonates, teriparatide is considered as a treatment option for the secondary prevention of an osteoporotic fragility fracture only if the woman either has an extremely low BMD or has a very low BMD plus multiple fragility fractures plus one or more age-independent risk factors.

7.4 Local clinical audits on the care of women who have experienced an osteoporotic fragility fracture also could 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 identifying high-risk patients, maintaining patient adherence with bisphosphonate drug therapy, educating patients about the condition and treatments, appropriate investigation and the involvement of the multiprofessional team in managing patients with osteoporosis.

8 Related guidance

8.1 NICE plans to publish the guidance *Bisphosphonates (alendronate, etidronate, risedronate) and selective oestrogen receptor modulators (raloxifene) for the primary prevention of osteoporotic fragility fractures in postmenopausal women* (publication date to be confirmed).

8.2 NICE plans to publish the guideline *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk* in February 2006.

8.3 NICE plans to publish the guideline *Falls: the assessment and prevention of falls in older people* in September 2004.

9 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 any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on this technology will be reviewed when a reliable method to quantify clinical risk factors becomes available or in October 2007 at the latest.

Andrew Stevens
Chair, Appraisal Committee
July 2004
Appendix 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 three times a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair, vice-chair and a number of other members between them attending meetings of all 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.

Dr Jane Adam
Radiologist, St George’s Hospital, London

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice, Staffordshire

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical sciences, University of Manchester

Professor David Barnett
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry
Consultant in Paediatric Intensive Care and Honorary Senior Lecturer, Department of Child Health, Leicester Royal Infirmary
Ms Sally Gooch
Director of Nursing, Mid-Essex Hospital Services NHS Trust, Chelmsford

Professor Trisha Greenhalgh
Professor of Primary Health Care, University College London

Miss Linda Hands
Clinical Reader in Surgery, University of Oxford

Professor Peter Jones
Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

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

Ms Joy Leavesley
Senior Clinical Governance Manager, Guy's and St Thomas' NHS Trust

Ms Ruth Lesirge
Previously Director, Mental Health Foundation, London

Dr George Levvy
Chief Executive, Motor Neurone Disease Association, Northampton

Ms Rachel Lewis
Staff Nurse (Nephrology) Hull Royal Infirmary

Dr Ruairidh Milne
Senior Lecturer in Public Health, National Coordinating Centre for Health Technology Assessment, University of Southampton

Dr Neil Milner
General Medical Practitioner, Sheffield

Dr Rubin Minhas
General Practitioner with a Special Interest in Coronary Heart Disease, Primary Care CHD Lead, Medway PCT and Swale PCT

Final Appraisal Determination: Bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone for secondary prevention of osteoporotic fragility fractures (July 2004)
Dr Gill Morgan
Chief Executive, NHS Confederation, London

Professor Philip Routledge
Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Mr Miles Scott
Chief Executive, Harrogate Health Care NHS Trust

Professor Mark Sculpher
Professor of Health Economics, University of York

Mr Malcolm Stamp
Chief Executive, Addenbrooke’s NHS Trust

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

Professor Andrew Stevens (Chair)
Professor of Public Health, University of Birmingham

Dr Norman Waugh
Department of Public Health, University of Aberdeen
Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by The University of Sheffield, School of Health and Related Research (ScHARR). Further analyses were undertaken by the NICE Decision Support Unit (DSU).


A 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 (ACD) and consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

V Manufacturer/sponsors:
- Alliance for Better Bone Health (Aventis Pharma Ltd and Proctor & Gamble Pharmaceuticals UK Ltd)
VI Professional/specialist and patient/carer groups:

- Age Concern England
- BackCare
- Bone & Tooth Society
- British Geriatrics Society
- British Society for Rheumatology (BSR) and Arthritis & Musculoskeletal Alliance (ARMA)
- Counsel & Care for the Elderly
- Department of Health
- Institute for Ageing and Health
- Long Term Medical Conditions Alliance
- Medical Women’s Federation
- National Osteoporosis Society
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society (PCR)
- Research Institute for the Care of the Elderly
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Society for Endocrinology
- The Society and College of Radiographers
- The Women’s Nutritional Advisory Service
VII Commentator organisations (without the right of appeal):
- NHS Quality Improvement Scotland
- National Collaborating Centre for nursing and supportive care
- Health Development Agency
- British National Formulary

B 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 the use of bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone for osteoporosis by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Juliet Compston, Reader and Honorary Consultant Physician, nominated by the Bone and Tooth Society
- Professor Cyrus Cooper, Professor of Rheumatology, Southampton General Hospital, nominated by the National Osteoporosis Society
- Dr R M Francis, Reader in Medicine (Geriatrics), Consultant Physician, Bone Clinic, Freeman Hospital, Newcastle upon Tyne, nominated by the British Geriatrics Society
- Mrs Jo Lye, Patient Advocate, nominated by the National Osteoporosis Society
- Dr C Moniz, Clinical Director, Department of Clinical Biochemistry, Osteoporosis Clinic, King’s College Hospital, London, nominated by the National Osteoporosis Society
- Jackie Parrington, Acting Director, National Osteoporosis Society, nominated by the National Osteoporosis Society
- Dr Peter Selby, Consultant Physician, Department of Medicine, Manchester Royal Infirmary, nominated by the Society for Endocrinology and the National Osteoporosis Society
Appendix C. Detail on criteria for audit of the use of bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

Possible objectives for an audit
An audit could be carried out to ensure the appropriateness of consideration of bisphosphonates, selective oestrogen receptor modulators (SERMs) and parathyroid hormone 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 had an osteoporotic fragility fracture in a reasonable time period for audit, for example, all those who are seen in a general practice or treated in a hospital in 6 months. Post-menopausal women with corticosteroid-induced osteoporosis should be excluded from this audit.

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, SERMs and parathyroid hormone are as follows.
### Criterion Standard Exception Definition of terms

| 1. For a woman aged 75 years or older who has had an osteoporotic fragility fracture, bisphosphonates are considered as a treatment option, without the need for DEXA scanning | 100% of women aged 75 years and older who have had an osteoporotic fragility fracture | A. The woman has a contraindication to bisphosphonates  
B. The woman is physically unable to comply with the special recommendations for use of bisphosphonates  
C. The woman is intolerant of bisphosphonates | Bisphosphonates include alendronate, etidronate or risedronate.  
An osteoporotic fragility fracture is a fracture that occurs as a result of mechanical forces that would not ordinarily cause fracture, for example, a force equivalent to a fall from a standing height or less.  
Contraindications include: hypocalcaemia or severe renal impairment (for risedronate and etidronate). Bisphosphonates should be used cautiously with women who have active upper gastrointestinal problems.  
See Summaries of Product Characteristics for a description of special recommendations for use of bisphosphonates.  
‘Intolerance to bisphosphonates’ is defined as oesophageal ulceration, erosion or stricture, or lower gastrointestinal symptoms, warranting discontinuation of treatment with a bisphosphonate.  
Clinicians will need to agree locally on how an osteoporotic fragility fracture and consideration of the treatment options, balancing the individual drug’s overall proven effectiveness profile against the tolerability profile, are documented for audit purposes. |

| 2. For a woman aged 65–75 years who has had an osteoporotic fragility fracture, bisphosphonates considered as treatment options if the woman has DEXA confirmed osteoporosis | 100% of women aged 65–75 years who have had an osteoporotic fragility fracture and DEXA confirmed osteoporosis | A. The woman has a contraindication bisphosphonates  
B. The woman is physically unable to comply with the special recommendations for use of bisphosphonates  
C. The woman is intolerant to bisphosphonates | See above for definitions of relevant terms.  
‘DEXA confirmed osteoporosis’ means a T-score below –2.5 SD. |
### 3. For a postmenopausal woman younger than 65 years who has had an osteoporotic fragility fracture, bisphosphonates are considered as treatment options if the woman has one of the following:

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<tbody>
<tr>
<td>a. a very low BMD or b. confirmed osteoporosis plus one or more additional age-independent risk factors</td>
</tr>
</tbody>
</table>

For a postmenopausal woman younger than 65 years who has had an osteoporotic fragility fracture, bisphosphonates are considered as treatment options if the woman has one of the following:

- a very low BMD
- confirmed osteoporosis plus one or more additional age-independent risk factors

100% of women aged younger than 65 years of age who have had an osteoporotic fragility fracture and who meet 3a or b.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. The woman has a contraindication to bisphosphonates</td>
</tr>
<tr>
<td>B. The woman is physically unable to comply with the special recommendations for use of bisphosphonates</td>
</tr>
<tr>
<td>C. The woman is intolerant of bisphosphonates</td>
</tr>
</tbody>
</table>

A. The woman has a contraindication to bisphosphonates

### 4. For a woman aged 75 years or older who has had an osteoporotic fragility fracture, raloxifene is considered as a treatment option, without the need for DEXA scanning if she meets any one of the following:

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. she has a contraindication to bisphosphonates or b. she is physically unable to comply with the special recommendations for use of bisphosphonates or c. she has had an unsatisfactory response to bisphosphonates</td>
</tr>
</tbody>
</table>

For a woman aged 75 years or older who has had an osteoporotic fragility fracture, raloxifene is considered as a treatment option, without the need for DEXA scanning if she meets any one of the following:

- she has a contraindication to bisphosphonates
- she is physically unable to comply with the special recommendations for use of bisphosphonates
- she has had an unsatisfactory response to bisphosphonates

100% of women aged 75 years and older who have had an osteoporotic fragility fracture and who meet 4a or b or c or d.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. The woman has a contraindication to the use of raloxifene</td>
</tr>
<tr>
<td>See above for definitions of relevant terms.</td>
</tr>
</tbody>
</table>

A very low BMD is a T-score of approximately –3 SD or below, established by a DEXA scan. ‘Additional age-independent risk factors’ are low body mass index (< 19 kg/m²); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; certain medical disorders independently associated with bone loss (such as chronic inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism or coeliac disease); conditions associated with prolonged immobility.

A. The woman has a contraindication to bisphosphonates

B. The woman is physically unable to comply with the special recommendations for use of bisphosphonates

C. The woman is intolerant of bisphosphonates

See above for definitions of relevant terms.

A very low BMD is a T-score of approximately –3 SD or below, established by a DEXA scan. ‘Additional age-independent risk factors’ are low body mass index (< 19 kg/m²); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; certain medical disorders independently associated with bone loss (such as chronic inflammatory bowel disease, rheumatoid arthritis, hyperthyroidism or coeliac disease); conditions associated with prolonged immobility.

‘Unsatisfactory response to bisphosphonates’ is defined as incurring another fragility fracture despite full adherence with treatment for a period of 1 year and evidence of a decline in BMD below the woman’s pre-treatment baseline.

Contraindications to raloxifene include any of the following: a history of venous thromboembolism, hepatic impairment, cholestasis, severe renal impairment, undiagnosed uterine bleeding, endometrial cancer or concurrent treatment for breast cancer, including adjuvant therapy.
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>d. she is intolerant of bisphosphonates</td>
<td>100% of women aged between 65 and 75 years who have had an osteoporotic fragility fracture and DEXA confirmed osteoporosis and who meet 5a or b or c or d</td>
<td>A. The woman has a contraindication to the use of raloxifene</td>
<td>See above for definitions of relevant terms.</td>
</tr>
<tr>
<td>5. For a woman aged between 65 and 75 years who has had an osteoporotic fragility fracture, raloxifene is considered as a treatment option if the woman has DEXA confirmed osteoporosis and if she meets any one of the following:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. she has a contraindication to bisphosphonates or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. she is physically unable to comply with the special recommendations for use of bisphosphonates or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. she has had an unsatisfactory response to bisphosphonates or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. she is intolerant of bisphosphonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. For a postmenopausal woman younger than 65 years who has had an osteoporotic fragility fracture, raloxifene is considered as a treatment option if the woman has one of the following:</td>
<td>100% of women aged younger than 65 years of age who have had an osteoporotic fragility fracture and who meet 6a or b and who meet 6c or d or e or f</td>
<td>B. The woman has a contraindication to the use of raloxifene</td>
<td>See above for definitions of relevant terms.</td>
</tr>
<tr>
<td>a. a very low BMD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
or
b. confirmed osteoporosis plus one or more additional age-independent risk factors
c. **and** if she meets any one of the following:
d. she has a contraindication to bisphosphonates or
e. she is physically unable to comply with the special recommendations for use of bisphosphonates or
f. she has had an unsatisfactory response to bisphosphonates or
g. she is intolerant of bisphosphonates

| 7. For a woman aged 65 years or older who has had an unsatisfactory response to bisphosphonates, teriparatide is considered as a treatment option only if the woman has the following: |
|---|---|---|
| a. an extremely low BMD **or**
b. a very low BMD plus multiple fragility fractures plus one or more age-independent risk factors | 100% of women aged 65 years or older who have had an unsatisfactory response to bisphosphonates and who meet 7a or b | A. The woman has a contraindication to the use of teriparatide |
|  |  | See above for definition of relevant terms. An extremely low BMD is a T-score of approximately −4 SD or below. ‘Multiple fragility fractures’ means more than 2 fragility fractures. ‘Age-independent risk factors’ are low body mass index (< 19 kg/m²); family history of maternal hip fracture before the age of 75 years; untreated premature menopause; conditions associated with prolonged immobility. |
**Calculation of compliance**

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

\[
\text{Compliance} = \left(\frac{\text{Number of patients whose care is consistent with the criterion} + \text{number of patients who meet any exception listed}}{\text{Number of patients to whom the measure applies}}\right) \times 100
\]

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.