NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

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

1 Guidance

This guidance relates only to the initiation of therapy for the secondary prevention of fragility fractures in postmenopausal women who have osteoporosis and have sustained a clinically apparent fragility fracture.

This guidance does **not** cover the following.

- The treatment of women who are contra-indicated to or, for whatever reason, have withdrawn from initial treatment.
- The use of alendronate, etidronate, risedronate, raloxifene, strontium ranelate or teriparatide for the secondary prevention of osteoporotic fractures in women with normal bone mineral density (BMD) (that is, women with a T-score* no more than one standard deviation [SD] below peak BMD).
- The use of these drugs in women who have osteopenia (that is, women with a T-score* between –1 and –2.5 SD).
- The use of these drugs for the secondary prevention of osteoporotic fractures in women who are on long-term systemic corticosteroid therapy.

NICE is developing a clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk', which will cover the treatment of women who are contra-indicated to or have withdrawn from initial treatment, who have osteopenia, and who are on

long-term corticosteroid therapy. This technology appraisal guidance should be read in the context of the clinical guideline when it is available.

This guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment have an adequate calcium intake and are vitamin D replete, calcium and/or vitamin D supplementation should be considered.

(*T-score relates to the measurement of BMD using axial [hip and/or spine] dual energy X-ray absorptiometry [DXA] scanning and is expressed as the number of SDs from peak BMD.)

1.1 Alendronate is recommended as a treatment option for the initiation of therapy for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who have a T-score of –2.5 SD or below. In women aged 75 years or older, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

When the decision has been made to initiate treatment with alendronate, the preparation prescribed should be chosen on the basis of the lowest acquisition cost available.

1.2 Etidronate, risedronate, raloxifene, strontium ranelate and teriparatide are not recommended for the initiation of therapy for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

1.3 Women who are currently receiving treatment with one of the drugs covered by this appraisal, but for whom initiation of therapy would not have been recommended according to sections 1.1 and 1.2 of this guidance, should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

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 the decrease in oestrogen production after the menopause accelerates bone loss to a variable degree.

2.3 Diagnosis of osteoporosis is based on a measurement of BMD, with reference to the number of SDs (T-score) from the BMD at peak bone mass.

- Normal: T-score of −1 SD or above.
- Osteopenia: T-score of between –1 and –2.5 SD.
- Osteoporosis: T-score of –2.5 SD or below.
- Established (severe) osteoporosis: T-score of –2.5 SD or below with one or more associated fractures.

2.4 T-score measurements vary depending on the site and method of investigation. Measurement of BMD using axial (hip and/or spine) DXA scanning can estimate fracture risk.

2.5 It is often estimated that more than 2 million women have osteoporosis (that is, have a T-score of –2.5 SD or below) in England and Wales. Osteoporosis is most common in older white women. After the menopause, the prevalence of osteoporosis increases markedly with age from approximately 2% at 50 years rising to more than 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 text). 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 that of a hip fracture, one in five. 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 to 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 can be associated with curvature of the spine and loss of height and can result in pain, breathing difficulties, gastrointestinal problems and difficulties in 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 related 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 osteoporosis. Some of these clinical factors are at least partly independent of BMD, and include parental history of hip fracture, alcohol intake of 4 or more units per day, and long-term systemic use of corticosteroids (the last factor is not covered in this guidance), and long-term rheumatoid arthritis.

2.12 Other factors known to be associated with low BMD include: low body mass index (defined as less than 22 kg/m^2); untreated premature menopause; medical conditions including ankylosing spondylitis, and Crohn's disease; and conditions that result in prolonged immobility.

2.13 A full review of risk factors associated with osteoporosis is being 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'.

3 The technologies

Bisphosphonates: alendronate, etidronate, risedronate

3.1 The bisphosphonates alendronate, etidronate and risedronate are inhibitors of bone resorption and increase BMD by altering osteoclast activation and function.

3.2 Alendronate is an oral bisphosphonate licensed in the UK as a once weekly preparation (70 mg) for the treatment of postmenopausal osteoporosis. It is also licensed at a daily dose of 10 mg for the treatment of osteoporosis in postmenopausal women to prevent fractures. Weekly non-proprietary alendronate (Teva Pharmaceutical Industries) costs £7.31 for four 70-mg tablets (excluding VAT, NHS Drug Tariff, 01 November 2006). At this price the drug cost for 1 year with the once weekly treatment is £95.03. Proprietary alendronate (Fosamax, Merck Sharp & Dohme) is priced at £22.80 (for four 70-mg tablets) and £23.12 (for a 28-tablet pack of 10-mg tablets) (excluding

VAT, British national formulary [BNF] edition 53). At these prices, the drug costs for 1 year are £301.39 for the daily (10 mg) tablets and £296.40 for the once weekly (70 mg) tablets. Costs may vary in different settings because of negotiated procurement discounts.

3.3 Etidronate (Didronel; Procter & Gamble Pharmaceuticals UK) 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 £21.12 (excluding VAT; BNF 53), which equates to a yearly cost of £85.65. Costs may vary in different settings because of negotiated procurement discounts.

3.4 Risedronate (Actonel; Procter & Gamble Pharmaceuticals UK) is an oral bisphosphonate licensed in the UK at a dosage of 5 mg/day or 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 a 28-tablet pack of 5-mg tablets and £20.30 for four 35-mg tablets (excluding VAT; BNF 53), which equates to yearly costs of £248.98 for daily treatment or £264.63 for once weekly treatment. Costs may vary in different settings because of negotiated procurement discounts.

3.5 Gastrointestinal side effects are common with oral bisphosphonates. In people with oesophageal abnormalities and other factors that 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 with water at the midpoint of a 4-hour fast (that is, 2 hours after and 2 hours before food, vitamins with mineral supplements [such as iron], calcium supplements, laxatives containing magnesium, or antacids containing calcium or aluminium).

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 (Evista; Eli Lilly and Company) is the only SERM licensed for the treatment of osteoporosis in postmenopausal women. The recommended dose is 60 mg/day. The prices of the 28- and 84- tablet packs are £17.06 and £59.59, respectively (excluding VAT; BNF 53), which equates to yearly costs of £222.39 and £258.93, respectively. Costs may vary in different settings because of negotiated procurement discounts.

3.9 Raloxifene is contraindicated in people with a history of venous thromboembolism (VTE), hepatic impairment, cholestasis, severe renal impairment, undiagnosed uterine bleeding or 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 (Protelos; Servier Laboratories) is a divalent strontium salt of ranelic acid (strontium is an element with properties similar to calcium). 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 taken daily as a suspension in water. The price of a 28-sachet pack is £25.60 (excluding VAT; BNF 53), which equates to a yearly cost of £333.71. Costs may vary in different settings because of negotiated procurement discounts.

3.11 The absorption of strontium ranelate is reduced by food, milk and products derived from milk. It should therefore be administered between meals, ideally at bedtime and preferably at least 2 hours after eating.

3.12 The SPC does not recommend strontium ranelate in patients with severe renal impairment and should be used with caution in patients at increased risk of VTE. 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 (Forsteo; Eli Lilly and Company) 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 in 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 53), which equates to a cost for 1 year of £3544.15.

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 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 (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The assessment group for this appraisal (School of Health and Related Research University of Sheffield [ScHARR]) 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, such as 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 trial arms had normal calcium levels (that is, normal serum concentrations) or adequate supplementation, and some studies also required additional dietary supplementation with vitamin D.

4.1.2 For this appraisal, reductions in RR 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 little evidence was available 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 whereas others used fractures that were identified radiographically. Vertebral fractures identified radiographically, which are termed 'radiographic fractures' or 'morphometric fractures', include both symptomatic and asymptomatic fractures. There are different definitions of a vertebral radiographic fracture, but those definitions that require a 20% reduction in vertebral height are generally recognised as producing more reliable 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, whereas 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. All the studies were conducted in women who had adequate levels of calcium, either from dietary intake or calcium supplementation.

4.1.5.2 Two studies, one comparing alendronate with oestrogen or with oestrogen and 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% versus 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 because it did not include 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, four RCTs, n = 7039), an RR of hip fracture of 0.62 (95% CI, 0.40 to 0.98, three RCTs, n = 7455), an RR of wrist fracture of 0.67 (95% CI, 0.34 to 1.31, four RCTs, n = 7931) and an RR for other non-vertebral fractures of 0.81 (95% CI, 0.68 to 0.97, six RCTs, n = 9973).

4.1.5.5 A post-hoc analysis of data from the largest study on alendronate, the FIT RCT (non-vertebral fracture population), suggested that alendronate may be less effective at reducing fractures in women with T-scores greater (that is, better T-scores) than –2.5 SD compared with women with osteoporosis. Results for T-scores greater than –2.5 SD were not statistically significant.

4.1.5.6 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 that indicate that approximately one third of alendronate users experience gastrointestinal adverse events. 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.

4.1.5.7 Prescription event monitoring studies in patients who were prescribed alendronate (n = 11,916) by GPs in England demonstrated a high incidence of dyspepsia, particularly in the first month of treatment.

Consultations for dyspepsia ranged from 32.2 per 1000 patient-months in the first month of treatment to 10.9 per 1000 patient-months in months 2 to 6. Because these studies lacked a comparator it is not possible to assess the extent to which these rates of upper gastrointestinal events may be above baseline levels in those not taking bisphosphonates.

4.1.5.8 One study reported health-related quality of life outcomes. At 12 months there were statistically significant improvements in the alendronate group compared with 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 or 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, study participants 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 cycles of etidronate 400 mg/day for 14 days, followed by calcium carbonate 1.25 g/day 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, three RCTs, n = 341), an RR of hip fracture of 0.50 (95% CI, 0.05 to 5.34, two RCTs, n = 180), and an RR for other non-vertebral fractures of 1.04 (95% CI, 0.64 to 1.69, four RCTs, n = 410). 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 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 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 other bisphosphonates.

4.1.6.5 The systematic review carried out by ScHARR identified a cohort study conducted in the UK that indicated that etidronate may be associated with a much lower rate of upper gastrointestinal adverse effects than alendronate or risedronate.

4.1.7 Risedronate

4.1.7.1 Seven RCTs of risedronate 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, three RCTs, n = 2301), an RR of hip fracture of 0.74 (95% CI,

0.59 to 0.93, three RCTs, n = 11,770), an RR of wrist fracture of 0.68 (95% CI, 0.43 to 1.08, two RCTs, n = 2439) and an RR for other non-vertebral fractures of 0.76 (95% CI, 0.64 to 0.91, five RCTs, n = 12,399).

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

4.1.7.4 Prescription event-monitoring studies in patients who were prescribed risedronate (n = 13,643) by GPs in England suggested a high incidence of dyspepsia, particularly in the first month of treatment. Consultations for dyspepsia ranged from 26.9 per 1000 patient-months in the first month of treatment to 8.1 per 1000 patient-months in months 2 to 6.

4.1.8 Alendronate and risedronate: meta-analysis

4.1.8.1 Pooled analysis of data from alendronate and risedronate studies, carried out by ScHARR in 2006, resulted in an RR of vertebral fracture of 0.58 (95% CI, 0.51 to 0.67, seven RCTs, n = 9340), an RR of hip fracture of 0.71 (95% CI, 0.58 to 0.87, six RCTs, n = 19,233), an RR of wrist fracture of 0.69 (95% CI, 0.45 to 1.05, six RCTs, n = 1037), and an RR for other non-vertebral fractures of 0.78 (95% CI, 0.69 to 0.88, 11 RCTs, n = 22,372).

4.1.9 Raloxifene

4.1.9.1 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 [MORE] study) was carried out in women with osteoporosis, of whom 37% had a vertebral fracture at entry, and a smaller study was conducted in women with established osteoporosis. Both compared raloxifene with placebo (in both studies, women in both arms received calcium and vitamin D). Both studies examined raloxifene at dosages of 60 mg/day (UK licensed dosage 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 further to 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 SD or lower (that is, worse), 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.

4.1.9.2 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, one RCT, n = 4551), an RR of hip fracture of 1.13 (95% CI, 0.66 to 1.96, two RCTs, n = 6971), an RR of wrist fracture of 0.89 (95% CI, 0.68 to 1.15, one RCT, n = 6828), and an RR for other non-vertebral fractures of 0.92 (95% CI, 0.79 to 1.07, one RCT, n = 6828).

4.1.9.3 The most serious adverse effect associated with raloxifene is the approximately three-fold increased risk of VTE. 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. The impact of raloxifene on cardiovascular disease is unclear, although there is evidence that it lowers fibrinogen, as well as both total and low-density lipoprotein (LDL) cholesterol levels (that is, serum concentrations), without increasing high-density lipoprotein (HDL) cholesterol.

4.1.9.4 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 of invasive breast cancer as 0.28 (95% CI, 0.17 to 0.46).

4.1.10 **Strontium ranelate**

4.1.10.1 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 with placebo, and provided calcium and vitamin D supplementation to ensure an adequate intake.

4.1.10.2 The Assessment Group reported the results of a published meta-analysis that resulted in an RR for vertebral fracture of 0.60 (95% CI 0.53 to 0.69, two RCTs, n = 6551) and an RR for all non-vertebral fractures (including wrist fracture) of 0.84 (95% CI 0.73 to 0.97, two 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, one RCT, n = 4932). A post-hoc subgroup analysis in women over 74 years of age 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, one RCT, n = 1977).

4.1.10.3 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 VTE and pulmonary embolism. This finding is being investigated further with the extension of ongoing studies and by post-marketing surveillance.

4.1.10.4 One study published results on health-related quality of life. It reported that strontium ranelate had quality of life benefits compared with placebo, as assessed by the QUALIOST osteoporosis-specific questionnaire and by the general health perception score of the short form (SF)-36 general scale.

4.1.11 **Teriparatide**

4.1.11.1 Three RCTs of teriparatide in postmenopausal women were considered: one small study compared teriparatide with alendronate in women with osteoporosis (but was not targeted at women with fractures), and two were placebo-controlled (although study participants 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.

4.1.11.2 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.

4.1.11.3 Data from a follow-up observational study cited in the manufacturer's submission (published in abstract form or available as an 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 the 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.

4.1.11.4 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% versus 19%, p = 0.012).

4.1.11.5 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.

4.1.12 Persistence and compliance

Bisphosphonates

4.1.12.1 Data from 14 RCTs indicated that between 81% and 100% of patients persisted with bisphosphonates in the first year of treatment, with lower rates of persistence of between 51% and 89% in the third year of treatment (eight RCTs).

4.1.12.2 A prescription event-monitoring study of patients who were prescribed alendronate (n = 11,916) by GPs in England indicated that 24% discontinued therapy within 1 year. In a similar study of patients prescribed risedronate (n = 11,742) in primary care in England, 30% appeared to have discontinued therapy within 6 months. In another 12 studies reviewed, persistence at 1 year ranged from 16% to 90%.

Raloxifene

4.1.12.3 US-based paid claims data suggested that only 18% of those initiating raloxifene therapy continued to take their medication uninterrupted and an

investigation of a pharmacy prescription database indicated that only 44% were continuing therapy at the end of year 2.

Strontium ranelate

4.1.12.4 Compliance data were reported for two RCTs of strontium ranelate and were similar for the strontium ranelate and placebo arms (ranging from 83% to 93%).

Teriparatide

4.1.12.5 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

Manufacturers' models

4.2.1 For proprietary alendronate, compared with no treatment, the manufacturer's model resulted in an incremental cost-effectiveness ratio (ICER) of £3135 per quality-adjusted life year (QALY) for 70-year-old women with a T-score below –1.6 SD. The manufacturer's model gave more favourable ICERs than the Assessment Group's 2003 model. This could be because the manufacturer's model was not adjusted for baseline fracture prevalence, or because it used different utilities for vertebral fractures, different efficacy data, different risk groups, and a longer time horizon.

4.2.2 For etidronate, compared with no treatment, the manufacturer calculated an ICER of £18,634 per QALY 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 ICER was for women with or without osteoporotic fragility fracture.

4.2.3 For risedronate, compared with no treatment, the manufacturer provided data from two models. The ICER derived from the manufacturer's own model was £577 per QALY for women aged 74 years. However, in the second model provided by the manufacturer, which was commissioned from an external body, the ICER was higher, varying from £35,800 at 60 years of age to £4800 per QALY at 80 years of age for women with a prior vertebral osteoporotic fragility fracture and a T-score of –2.5 SD. For women at slightly higher risk of fracture, the ICERs were £18,600 per QALY or less for all age groups. The ICER calculated by the manufacturer's own model is difficult to verify from the information given. The ICERs generated by the second model are more consistent with the figures provided by the Assessment Group's 2003 model, although they do differ somewhat. This may be because of different cost and RR inputs.

4.2.4 For raloxifene, compared with no treatment, the manufacturer provided data for different age groups and different risk levels. All of the analyses included the breast cancer benefits. It was not clear how the different risk levels were defined. The ICERs ranged from £12,000 to £22,000 per QALY and were slightly more favourable than the Assessment Group's analysis, even when the Assessment Group included the breast cancer benefits. In the Assessment Group's 2003 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 was not adjusted for baseline fracture prevalence, and included different utilities for vertebral fractures, different efficacy data, different risk groups, and a longer time horizon than the Assessment Group's model.

4.2.5 For strontium ranelate, compared with no treatment, the manufacturer provided two models: one developed in-house and the other commissioned from an external body. The first model showed that, for women aged over 75 years with previous fractures and a T-score of –2.5 SD, strontium

ranelate was cost-effective at a maximum acceptable incremental cost-effectiveness ratio of £30,000 per QALY. The results of this model are comparable with those generated by the Assessment Group's 2005 model. The second model resulted in an ICER of £6341 per QALY for 70-year-old women with a previous vertebral fracture and a T-score of –2.5 SD, decreasing to £5002 per QALY at 80 years of age. The manufacturer's results were more favourable than the Assessment Group's 2005 results because different modelling assumptions were used. For example, fewer health-state transition possibilities were incorporated. Compared with the Assessment Group's model, the manufacturer's model used more favourable hip-fracture efficacy data from a subgroup of patients aged over 74 years, and slightly more favourable efficacy data for wrist and proximal humerus fracture. Higher hip-fracture costs were used in the manufacturer's model.

4.2.6 For teriparatide, compared with no treatment, the manufacturer provided ICERs for women aged 69 years. For women with fractures that had occurred more than 6 months previously (historical fracture), the ICER was £35,400 per QALY and for women with a more recent fracture the ICER was £28,863 per QALY. The manufacturer supplied additional economic analyses with ICERs of £18,845 and £12,106 per QALY 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 2003 model differed in a number of assumptions. The manufacturer's model was not adjusted for baseline fracture prevalence and used different utilities. The Assessment Group's 2003 model used more favourable assumptions on the duration of sustained efficacy after the end of treatment.

The Assessment Group's model

4.2.7 The Assessment Group provided a cost–utility model with two components: first it calculated absolute fracture risk from the epidemiological literature

summarised in a World Health Organization (WHO) draft report, then it applied RR reductions for fracture taken from the meta-analysis described in section 4.1.8). A single estimate of efficacy was used for alendronate and risedronate based on pooled data for these two drugs. Following advice from the osteoporosis Guideline Development Group, it was assumed that RRs remain constant across all ages, T-scores and fracture status. The most recent analyses carried out by ScHARR were based on the price of non-proprietary alendronate in November 2006 (£95.03 per year).

4.2.8 All osteoporotic fractures in women aged 50 years and older 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 for RRs spanned unity, it was assumed that there was no effect of treatment, except in the case of strontium ranelate in a subgroup of older women. In this case, an RR of 0.85 for hip fracture was used to acknowledge an effect reported in a subgroup of the study. The model used UK-specific epidemiological data on femoral neck BMD.

4.2.9 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 of treatment with sustained efficacy plus 5 years of linear decline to no effect. In the base case, vertebral-fracture utility was assumed to be lower than hip fracture utility. 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, and 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: this reflects current clinical practice in the UK.

4.2.10 The model included an assumption about the costs and disutility associated with treatment-related side effects for all drugs, based on the findings of prescription event-monitoring studies in patients treated with alendronate. For the base case, the model assumed 50% persistence with therapy. In addition to the base case, the Assessment Group undertook a number of sensitivity analyses using alternative assumptions including: persistence with therapy; reduction of the efficacy of the drugs at reducing the risk of fracture associated with risk factors other than age, previous fracture and low BMD to 0% or 50% (with a consequent upward adjustment of the RR for the risk factors age, previous fracture and low BMD); disutility of vertebral fracture; updated fracture costs; and the disutility and costs of treatment-related side effects. It was assumed that women who experience bisphosphonate-related side effects had 91% of the utility of women who did not have such side effects. In the base case this was applied to 2.35% of patients per first treatment month and 0.35% of patients thereafter. In the case of strontium ranelate, the effect on VTE was not included in the model. Discount rates of 6% per year for costs and 1.5% per year for health benefits were applied, in accordance with NICE methods relevant for this appraisal.

4.2.11 For raloxifene, the cost effectiveness was initially 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; neither the risk of VTE nor the effect on cardiovascular events was incorporated into the model.

4.2.12 A number of clinical risk factors were aggregated and quantified as absolute risk. The model used an unpublished fracture-risk algorithm currently in development under the auspices of the WHO. The clinical risk factors included body mass index, previous fracture, previous or current 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. Using these risk ratios, absolute risk of fracture can be calculated.

4.2.13 The estimates of cost effectiveness were generated for different levels of absolute risk derived from a large number of combinations of T-scores (in bands 0.5 SD wide), ages and risk factors. For practical reasons relating to the number of potential combinations, single-point RRs of fracture, calculated from the log-normal efficacy distributions, were used in the model. Results were presented for population groups categorised according to age, T-score and number of clinical risk factors.

4.2.14 Women with a fracture who present to clinicians will require a DXA scan for osteoporosis to be established. Therefore, the assessment group also estimated the impact of DXA scanning on the cost effectiveness of the drugs. This required both a calculation of the ICER for treatment and a calculation of the distribution of risk assessment cost over the population that would benefit from treatment. A net-benefit approach was used to do this. The net-benefit approach is analogous to the more traditional cost-per-QALY approach, but also requires a value of willingness to pay (WTP) for an additional QALY. For the calculation of the net benefit of an intervention, the WTP is first multiplied by the incremental QALY associated with the intervention, and then the incremental cost associated with the intervention is subtracted. For this appraisal, the total net benefit for each age group and DXA scanning approach was calculated by subtracting the cost of DXA scanning from the net benefit of treating all women who can be treated cost effectively.

4.2.15 A stepped net benefit approach was used to ascertain, in reverse order, the cost effectiveness of DXA scanning and treatment of women with a prior fracture. Two WTP values, £20,000 or £30,000 per QALY, were applied in the modelling.

4.2.15.1 **Step 1**. ICERs for treatment versus no treatment were calculated for each intervention by combining age, T-score and clinical risk factors (see section 4.2.12). The net benefit of treatment per woman was calculated using the following formula: Net benefit = £30,000 (or £20,000) × incremental QALYs – incremental costs. For women for whom the ICER of treatment was more than £30,000 (or £20,000) per QALY, the net benefit was set to zero.

4.2.15.2 **Step 2.** The net benefit per woman was multiplied by the number of women in the population estimated to fall within each age/T-score/clinical risk factor group (based on the data used to develop the algorithm prepared for the WHO). The net benefits for each group were then added together to give a total net benefit of treatment for women with no, one, two or three clinical risk factors within each age group.

4.2.15.3 **Step 3.** The cost of DXA scanning all of the women in each age/clinical risk factor group was subtracted from the net benefit of treatment for that group (calculated as described in step 2; section 4.2.15.2). This provides the net benefit of treatment and DXA scanning for the group, assuming that the number of clinical risk factors is known. A positive net benefit indicates that DXA scanning of women in that age/clinical risk factor group and treating those groups of women in whom the ICER of treatment is £30,000 (or £20,000) or less provides an ICER of the entire strategy of less than £30,000 (or £20,000) per QALY.

4.2.15.4 **Step 4.** When the resulting values of net benefit of treatment and scanning were negative they were set to zero. For each age group, the total net benefit of scanning and treatment was calculated by adding together the net benefits for each age/clinical risk factor group. The cost of opportunistic assessment for all women in this age group was then subtracted to give the net benefit of risk assessment, scanning and treatment. A positive net benefit indicates an ICER of less than £30,000 (or £20,000) per QALY for risk assessment, DXA scanning and treating

women (at a specific T-score related to the ICER for treatment only) of that particular group. Cost per QALY data were presented for each strategy.

The Assessment Group's model: results for alendronate

4.2.16 The Assessment Group calculated ICERs (cost per QALY using alendronate compared with no treatment) without identification costs for all age, T-score and clinical risk factor combinations. The cost per QALY, compared with no treatment, became more favourable with increasing age and number of risk factors and decreasing T-score (that is with increasing annual absolute risk of fracture).

4.2.17 The Assessment Group presented the results of the economic analyses in the form of identification and treatment strategies (based on age, T-score and number of clinical risk factors) that resulted in an ICER of £30,000 or less (cost per QALY compared with no treatment). The analyses presented included the following assumptions: persistence at 5 years set to 50%; the efficacy of bisphosphonates on fracture risks associated with factors other than age, BMD and previous fracture status set to 0% and alternatively at 50% of that observed for the total population in the trials (with a consequent upward adjustment of the RR associated with age, BMD and previous fracture); costs set to health resource group values including home-help costs; utility multiplier associated with vertebral fracture set to 0.792 in the first year of fracture (as for hip fracture) and 0.909 in subsequent years; costs of bisphosphonate-related gastrointestinal symptoms incurred over 5 years; utility multiplier associated with bisphosphonate-related gastrointestinal symptoms set to 0.91 (included utility losses for non-compliant patients); and alendronate at a cost of £95.03 per year.

4.2.18 When assuming that the efficacy of bisphosphonates on fracture risk associated with risk factors other than BMD and prior fracture was 50% (see section 4.2.10), the model produced the following results for a WTP of £30,000 per QALY.

- Women aged 50–54 years with one clinical risk factor would receive a DXA scan and those with osteoporosis would receive alendronate (cost of strategy per QALY = £27,422).
- All women aged 55 years or above would receive a DXA scan and those with osteoporosis would receive alendronate (cost of strategy per QALY = £22,689 for age 55–59 years, declining with increasing age).

4.2.19 When assuming that 24% of women were experiencing bisphosphonate-related side effects in the first treatment month and 3.5% of women thereafter and assuming that the efficacy of bisphosphonates on fracture risk associated with risk factors other than BMD and prior fracture was 50%, the model produced the following results for a WTP of £30,000 per QALY.

- Women aged 50-54 years would not receive treatment (cost of strategy per QALY greater than £30,000).
- Women aged 55–59 years with one clinical risk factor would receive a DXA scan and those with osteoporosis would receive alendronate (cost of strategy per QALY = £26,186).
- All women aged 60 years or older would receive a DXA scan and those with osteoporosis would receive alendronate (cost of strategy per QALY = £22,773 for age 60–64 years, declining with increasing age).

The Assessment Group's model: results for the other drugs

4.2.20 Risedronate, raloxifene and strontium ranelate were dominated by alendronate (based on the price of £95.03 per year for alendronate); that is, these three drugs have a higher acquisition cost than alendronate, but are not more efficacious. In the original modelling, etidronate's cost-effectiveness was comparable to non-proprietary alendronate, but the calculations were based on a weaker clinical evidence base than for alendronate. Therefore the modelling for etidronate was not updated following the most recent price reduction of alendronate. In an analysis prior to the latest price reduction for

non-proprietary alendronate, teriparatide was directly compared with pooled alendronate and risedronate and was found to have an ICER of more than £1millon.

4.2.21 For risedronate, raloxifene, strontium ranelate and teriparatide, additional analyses were conducted to explore identification and treatment strategies that could be cost effective for these interventions when compared with no intervention. All results showed less favourable cost effectiveness than non-proprietary alendronate. For example, when assuming that 24% of women were experiencing treatment-related side effects in the first treatment month and 3.5% of women thereafter and assuming that the efficacy of the drugs on risk factors other than BMD and prior fracture was 50%, the ICER for risedronate was over £30,000 per QALY for women under the age of 60 years (and for all age groups is dominated by non-proprietary alendronate); the ICER for raloxifene was over £30,000 per QALY for all age groups, the ICER for strontium ranelate was over £30,000 per QALY for women under the age of 70 years, and the ICER for teriparatide was over £30,000 per QALY for women under the age of 70 years.

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, strontium ranelate, raloxifene and teriparatide, having considered evidence on the nature of the condition and the value placed on the benefits of these drugs by people with osteoporosis, those who represent them, and clinical experts. It also considered the consultation comments received in response to its previous appraisal consultation document and the extra analysis undertaken by ScHARR in November 2006. It remained mindful of the need to ensure that its advice took account of the effective use of NHS resources. The Committee considered that women who have already sustained an osteoporotic fracture constitute a different population from the primary prevention population, who are well and asymptomatic.

4.3.2 The Committee considered the extent to which NICE technology appraisal 87 should be updated in the light of the introduction of a new drug (strontium ranelate), new pricing for alendronate and etidronate, and new cost-effectiveness modelling developed as part of the technology appraisal on primary prevention.

4.3.3 The Committee considered the clinical effectiveness data for all the bisphosphonates (alendronate, etidronate and risedronate), strontium ranelate, raloxifene and teriparatide. It noted that all these drugs have proven efficacy in reducing the incidence of vertebral fragility fractures in women with osteoporosis, but that there were differences between the drugs as to the degree of certainty that treatment results in a reduction in hip fracture (considered a crucial goal in osteoporosis management). In the cases of alendronate and of risedronate, it was accepted that there was sufficiently robust evidence to suggest a reduction in hip fracture risk. The Committee noted that the available RCTs for etidronate were of insufficient size to show statistically significant reductions in hip fracture risk, but that observational data lent support to a reduction in hip fracture risk.

4.3.4 The Committee 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 risk. The Committee was also aware of 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 years who have a T-score of –2.4 SD or below.

4.3.5 The Committee noted that the evidence for raloxifene showed an effect on vertebral fracture, but did not show any effect on hip fractures. In addition, there is evidence for a beneficial side effect of raloxifene on the incidence of breast cancer.

4.3.6 The Committee noted that teriparatide was effective in preventing vertebral and grouped non-vertebral fractures in women with osteoporosis who have

had a fracture, 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, and the high dose of teriparatide used. Therefore it considered that the evaluation of the overall advantages of teriparatide over bisphosphonates requires more research to establish relative clinical effectiveness.

4.3.7 The Committee noted that fracture risk is clearly related to age, low BMD and previous fracture. The Committee accepted that most other risk factors (see section 2.11 and 2.12) were likely to be associated with an increased fracture risk. The Committee was concerned that there was not sufficient evidence for a proven treatment effect on fracture risk related to risk factors other than low BMD, age and prior fracture. The Committee therefore concluded that preventative drug therapy should be targeted at women whose absolute risk of fracture is driven by low BMD and age, and that the recommendations should be made on the basis of age and BMD in the form of T-scores below which treatment is recommended.

Cost-effectiveness modelling

4.3.8 The Committee acknowledged the efforts of the Assessment Group to build on the model used previously, particularly in using so-far unpublished and complex WHO data to calculate transition probabilities and to model the identification approaches. The Committee was concerned that there was no evidence for a proven treatment effect on fracture risk related to risk factors other than low BMD, prior fracture and age (see section 4.3.7). However, the Committee concluded that the Assessment Group's model was likely to give the best estimates of cost effectiveness because it used data from a wide age range (age 50–75 years and older), and was updated to use all fracture sites, 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.

4.3.9 The Committee discussed the assumptions underpinning the economic modelling undertaken by the Assessment Group. It noted that the most recent modelling explored some of the uncertainties identified by the Committee surrounding the results of the previous modelling; these related to the costs and disutility associated with treatment-related side effects and to non-persistence with therapy in a proportion of patients. The Committee also noted the effect of the recent price reductions for non-proprietary alendronate (70 mg weekly dose) on the cost effectiveness of these drugs.

4.3.10 The Committee compared the base-case assumptions with those that were varied in the one-way sensitivity analyses and identified the assumptions that it considered most credible. The Committee noted that the fracture costs used in the base-case analysis were those used in the original assessment report developed in 2003 and considered that these were likely to be outdated. The Committee agreed that costs based on health resource groups, including home-help costs, were likely to provide the most accurate reflection of the cost of fractures to the NHS and personal social services, and it decided to incorporate these costs into the base-case analysis.

4.3.11 The Committee considered the utility multiplier for the first year after a vertebral fracture used in the base-case analysis and noted that it was considerably lower than that for a hip fracture. Although the Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, it considered that it was implausible that this would so greatly outweigh the utility decrement associated with a hip fracture. The Committee therefore considered it reasonable to assume that the disutility in the first year after a vertebral fracture was equivalent to the disutility in the first year after a hip fracture and decided to include this assumption in the base-case analysis.

4.3.12 The Committee was not persuaded that the drugs under consideration had been unequivocally shown to reduce fracture risk that was attributable to risk factors not mediated through low BMD and age. The Committee concluded that the uncertainty surrounding the efficacy of the drugs on risk factors not mediated through low BMD and age should be factored into its decision-making by using an analysis that assumed 50% efficacy of the drugs on fractures associated with risk factors other than age and low BMD. Although the Committee recognised that 50% was necessarily an arbitrary figure, the use of either 0% or 100% were both considered extreme and less plausible. In the analysis accepted by the Committee, the assumption of 50% efficacy of the drugs on fractures associated with other risk factors was adjusted by using a correspondingly greater efficacy for fractures associated with the key risk factors: age, BMD and prior fracture.

4.3.13 The Committee discussed a number of concerns surrounding other issues that are not represented in the model but that may have had an impact on the cost-effectiveness estimates. These included: possible long-term adverse effects of bisphosphonates on the formation of new bone; the likelihood that DXA scanning outside a clinical trial environment would not be as effective as in the clinical trials; and the possibility that the proportion of people who experience side effects may exceed the model's base-case assumptions. Finally, the Committee noted that current discount rates used by the Treasury, the Department of Health and NICE result in a cost-effectiveness calculation less favourable to the drugs than the discount rates used in the analysis considered by the Committee. Although a quantitative analysis of the uncertainties surrounding all these issues was not available, the Committee agreed that these uncertainties could be approximated through the sensitivity analysis for side effects (see 4.2.19).

Initiation of bisphosphonates: alendronate

4.3.14 The Committee considered the results of the economic model following the price reduction for non-proprietary alendronate, the newly included

assumptions and the sensitivity analyses (see sections 4.3.9 to 4.3.12) and observed that, for alendronate, treatment strategies might be considered cost effective in postmenopausal women with osteoporosis. This led the Committee to conclude that alendronate (based on the price of £95.03 per year) would be an appropriate use of NHS resources for the initiation of secondary preventative therapy in postmenopausal women with fragility fractures and confirmed osteoporosis (a T-score of –2.5 or below). The Committee was advised by the clinical experts that in women aged 75 years or older with a prior fracture, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

4.3.15 The Committee noted that the prices of different brands of alendronate vary greatly and concluded that alendronate should be prescribed on the basis of the lowest acquisition cost available.

4.3.16 The Committee discussed the possible treatment options available when alendronate is contraindicated at the point of initiation of therapy or when a woman is intolerant to alendronate, despite reasonable measures to support continuation of alendronate therapy. The Committee considered that all other treatment options (etidronate, risedronate, raloxifene, strontium ranelate and teriparatide) have higher acquisition costs and/or different effectiveness profiles, which would reduce the cost effectiveness of prevention therapy if these drugs were used. The Committee noted that the forthcoming NICE clinical guideline on osteoporosis would incorporate recommendations on the clinical and cost effectiveness of treatment pathways associated with contraindication or intolerance to, or failure of effectiveness of, alendronate.

Initiation with drugs other than alendronate: risedronate, etidronate, strontium ranelate, raloxifene or teriparatide

4.3.17 The Committee noted that risedronate was dominated by alendronate (based on the price of £95.03 per year for alendronate); that is, risedronate has a greater acquisition cost than alendronate but is not more efficacious. The Committee did not consider risedronate to be cost-effective for the initiation of

therapy for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

4.3.18 The Committee noted that etidronate was of comparable cost effectiveness to alendronate (based on the price of £95.03 per year for alendronate). However, the Committee took into account the concerns of clinical specialists and consultees surrounding the clinical evidence base for etidronate, and agreed that etidronate could not be considered to be an equivalent alternative to alendronate for the initiation of therapy for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

4.3.19 The Committee did not accept the estimate of efficacy for strontium ranelate in preventing hip fracture from the post-hoc subgroup analysis, but accepted the statistically non-significant RR of 0.85 for hip fracture to acknowledge an effect on this important type of fracture. The Committee noted that strontium ranelate was dominated by alendronate (based on the price of £95.03 per year for alendronate); that is, strontium ranelate has a greater acquisition cost and is not more efficacious. Therefore, the Committee did not consider strontium ranelate to be cost-effective for the initiation of therapy for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

4.3.20 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 particularly to younger post-menopausal 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 increased risk of VTE (see 4.1.9.3).

4.3.21 The Committee noted that a higher proportion of the overall benefit associated with raloxifene 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 initiation of therapy for the secondary prevention of osteoporotic fragility fractures.

- 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 breast cancer prevention.

4.3.22 The Committee noted that raloxifene was dominated by alendronate (based on the price of £95.03 per year for alendronate): that is, raloxifene has a greater acquisition cost and is not more efficacious. Therefore, the Committee did not consider raloxifene to be a cost-effective use of NHS resources for the initiation of therapy for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

4.3.23 The Committee noted the very high ICER for teriparatide when compared with pooled alendronate and risedronate from an analysis carried out by ScHARR prior to the latest price reduction for alendronate. The Committee concluded that this ICER for teriparatide would be even higher when compared to alendronate at the most recent price of £95.03 per year. Therefore, the Committee did not consider teriparatide to be a cost-effective use of NHS resources for the initiation of therapy for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

Calcium and vitamin D prerequisites for treatment

4.3.24 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 guidance, all participants were said to have adequate calcium and vitamin D levels. The Committee appreciated that the general population, particularly the elderly population, cannot be assumed to have an adequate dietary intake of calcium and vitamin D. It was also considered important to note that adequate levels (normal serum concentrations) 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 to women who receive osteoporosis treatment unless clinicians are confident that the women have an adequate calcium intake and are vitamin D replete. The Committee suggested that the forthcoming clinical guideline could specify how such assessment should be made and what supplementation should be prescribed.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal

guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). *[Note: tools will be available when the final guidance is issued]* **[List to be added]**

6 Recommendations for further research

6.1 Given the evidence that the benefits of one of the bisphosphonates (alendronate) may continue for several years after the end of treatment, the Committee recommends that research should be carried out to define the optimal duration of treatment with individual bisphosphonates.

6.2 The Committee recommends research into the long term effects of bisphosphonates on bone quality, given the inhibitory effects on bone resorption of these drugs.

6.3 There is some evidence that strontium ranelate may interfere with the results of DXA scanning because it has a higher molecular weight than calcium. It may also affect the measurement of calcium levels in the blood or urine. This could have implications in the clinical care setting and further research in this area is recommended.

7 Related NICE guidance

- 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 87. Available from: www.nice.org.uk/TA087

- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal (publication [TBC]).

- Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. NICE clinical guideline *(*publication [TBC]).

8 Review of guidance

8.1 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.

8.2 The guidance on this technology will be considered for review in July 2010.

Andrew Stevens
Chair, Appraisal Committee
June 2007

Appendix A. Appraisal Committee members, guideline representatives and NICE project team

A. Appraisal Committee members

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, each with a chair and vice-chair. 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.

Professor Keith Abrams (2006 - 2007)
Professor of Medical Statistics, University of Leicester

Ms Julie Acred (2004 - 2005)
Chief Executive, Derby Hospitals NHS Foundation Trust

Dr Jeff Aronson (2006 - 2007)
Reader in Clinical Pharmacology, Radcliffe Infirmary

Dr Darren Ashcroft (2004 – 2007)
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (2004 – 2007)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry (2004 – 2007)

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor Stirling Bryan (2006 - 2007)

Director of the Health Economics Facility, University of Birmingham

Mr Brian Buckley (2004 – 2006)

Vice Chairman, InContact

Professor John Cairns (2006 - 2007)

Public Health and Policy, London School of Hygiene and Tropical Medicine

Professor David Chadwick (2005 – 2006)

Professor of Neurology, Walton Centre for Neurology and Neurosurgery

Dr Peter I Clark (2004 – 2006)

Honorary Chairman, Association of Cancer Physicians

Ms Donna Covey (2004 – 2005)

Chief Executive, Asthma UK

Dr Mike Davies (2004 – 2006)

Consultant Physician, University Department of Medicine and Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips (2004 – 2006)

Public Affairs Manager, Medtronic Ltd

Professor Jack Dowie (2004 – 2007)

Health Economist, London School of Hygiene and Tropical Medicine

Professor Trisha Greenhalgh (2004 – 2005)

Professor of Primary Health Care, University College London

Lynn Field (2006 - 2007)

Nurse Director, Pan Birmingham Cancer Network

Professor Gary A. Ford (2004 – 2005)

Proefessor of Pharmacology of Old Age/Consultant Physician, Royal Victoria Infirmary, Newcastle upon Tyne

Professor Christopher Fowler (2006 - 2007)

Professor of Surgical Education, University of London

Dr Fergus Gleeson (2004 – 2007)

Consultant Radiologist, Churchill Hospital

Ms Sally Gooch (2004 – 2007)

Former Director of Nursing & Workforce Development, Mid Essex Hospitals Services NHS Trust

Mrs Barbara Greggains (2006 - 2007)

Lay Member

Mr Sanjay Gupta (2005 - 2007)

Stroke Services Manager, Basildon and Thurrock Universities Hospitals NHS Trust

Ms Linda Hands (2004 - 2005)

Consultant Vascular Surgeon, John Radcliffe Hospital, Oxford

Professor Philip Home (2005 – 2006)

Professor of Diabetes Medicine, Universities of Newcastle upon Tyne

Dr Peter Jackson (2005 – 2006)

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones (2004 – 2006)

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

Professor Robert Kerwin (2004 – 2005)

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

Dr Mike Laker (2005 – 2007)

Medical Director, Newcastle Hospitals NHS Trust

Ms Joy Leavesley (2004)

Senior Clinical Governance Manager, Whittington Hospital

Dr Ruth Lesirge (2004)

Lay Member

Ms Rachel Lewis (2004 – 2006)

Nurse Advisor to the Department of Health

Mr Terence Lewis (2006 – 2007)

Mental Health Consultant, National Institute for Mental Health in England

Dr George Levvy (2005 – 2006)

Lay Member

Professor Gary McVeigh (2006 - 2007)

Professor of Cardiovascular Medicine, Queens University, Belfast

Professor Jonathan Michaels (2004 – 2006)

Professor of Vascular Surgery, University of Sheffield

Dr Ruairidh Milne (2004 – 2007)

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

Dr Neil Milner (2004 – 2007)

General Medical Practitioner, Tramways Medical Centre, Sheffield

Dr Rubin Minhas (2004 – 2007)

General Practitioner, CHD Clinical Lead, Medway PCT

Dr John Pounsford (2006 – 2007)

Consultant Physician, North Bristol NHS Trust

Dr Rosalind Ramsay (2006 – 2007)

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

Dr Christa Roberts (2006 – 2007)

UK Country Manager, Abbott Vascular

Dr Stephen Saltissi (2006 – 2007)

Consultant Cardiologist, Royal Liverpool University Hospital

Mr Miles Scott (2004 – 2006)

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Lindsay Smith (2005 – 2007)

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith (2006 – 2007)

Corporate lead, finance, West Sussex PCT

Mr Cliff Snelling (2006 – 2007)

Lay Member

Mr Malcolm Stamp (2004)

Chief Executive, Addenbrookes NHS Trust

Dr Ken Stein (2004 – 2007)

Senior Lecturer in Public Health, Peninsula Medical School, University of Exeter

Professor Andrew Stevens (Chair) (2004 – 2007)

Professor of Public Health, University of Birmingham

Dr Rod Taylor (2006 – 2007)

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter & Plymouth

B. Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing the Institute's clinical guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

Professor Juliet Compston

Professor of Bone Medicine, University of Cambridge School of Clinical Medicine and Addenbrooke's NHS Trust

Dr Peter Selby

Consultant Physician, Central Manchester and Manchester Children's University Hospitals NHS Trust

Professor David Barlow

Executive Dean of Medicine, University of Glasgow

C. NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ruaraidh Hill and Emma Pugh

Technical Leads

Elisabeth George

Technical Adviser

Reetan Patel

Project Manager

Appendix B. Sources of evidence considered by the Committee

A The assessment reports for this appraisal were prepared by The University of Sheffield, School of Health and Related Research (ScHARR).

- Stevenson M (2006). Analyses of cost-effectiveness incorporating alendronate price reduction. Sheffield: School of Health and Related Research (ScHARR).
- Stevenson M, Lloyd Jones M, Davis S et al (2006) Analyses of the cost-effectiveness of pooled alendronate and risedronate, compared with strontium ranelate, raloxifene, etidronate and teriparatide. Sheffield: School of Health and Related Research (ScHARR).
- Lloyd Jones M and Wilkinson A (2006) Adverse effects and persistence with therapy in patients taking oral alendronate, etidronate or risedronate: systematic reviews. Sheffield: School of Health and Related Research (ScHARR).
- Stevenson M, Davis S, Lloyd Jones M and Beverley C (2005). Strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Sheffield: School of Health and Related Research (ScHARR).
- Stevenson M, Davis S (2005). Addendum to the Assessment Report: The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Sheffield: School of Health and Related Research (ScHARR).
- Stevenson M, Davis S (2005). Addendum to the Assessment Report: Analyses of the cost-effectiveness of pooled alendronate and risedronate, compared with strontium ranelate, raloxifene, etidronate and

teriparatide Sheffield: School of Health and Related Research (ScHARR).

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report. and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have 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
- TEVA

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
- Roche Pharmaceuticals Ltd
- Nycomed UK Ltd
- Welsh Assembly Government

C The following individuals were selected from clinical specialist 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 secondary prevention of osteoporotic fractures in postmenopausal women by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also 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 of Bone Medicine, University of Cambridge School of Clinical Medicine and Addenbrooke's NHS Trust – clinical specialist nominated by the Royal College of Physicians
- Dr R.M. Francis, Reader in Medicine (Geriatrics) and Honorary Consultant Physician, British Geriatrics Society – clinical specialist nominated by the British Geriatrics Society and the National Osteoporosis Society
- Dr Caje Moniz, Consultant and Clinical Director, King's Healthcare NHS Trust – clinical specialist nominated by the National Osteoporosis Society
- Dr Peter Selby, Consultant Physician, Central Manchester and Manchester Children's University Hospitals NHS Trust – clinical specialist nominated by the Society of Endocrinology and the National Osteoporosis Society