

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final appraisal determination

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

#### 1 Guidance

This guidance relates only to treatments for the primary prevention of fragility fractures in postmenopausal women who have osteoporosis. Osteoporosis is defined by a T-score<sup>1</sup> of  $-2.5$  standard deviations (SD) or below on dual-energy X-ray absorptiometry (DXA) scanning. However, the diagnosis may be assumed in women aged 75 years or older if the responsible clinician considers a DXA scan to be clinically inappropriate or unfeasible.

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 meet these criteria, calcium and/or vitamin D supplementation should be considered.

NICE is developing a clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' (see [www.nice.org.uk](http://www.nice.org.uk)). This

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<sup>1</sup> T-score relates to the measurement of bone mineral density (BMD) using central (hip and/or spine) DXA scanning, and is expressed as the number of standard deviations (SD) from peak BMD.

technology appraisal guidance should be read in the context of the clinical guideline when it is available.

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

- The treatment of women who have sustained a clinically apparent osteoporotic fragility fracture (for recommendations for the treatment of women with a prior osteoporotic fragility fracture, see the accompanying NICE technology appraisal, 'Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women').
- The use of alendronate, etidronate, risedronate, raloxifene or strontium ranelate for the primary prevention of osteoporotic fragility fractures in women with normal bone mineral density (BMD) or osteopenia (that is, women with a T-score between  $-1$  and  $-2.5$  SD below peak BMD).
- The use of these drugs for the primary prevention of osteoporotic fragility fractures in women who are on long-term systemic corticosteroid treatment.

The latter two groups will be covered within future guidance produced by the Institute.

1.1 Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in the following groups:

- Women aged 70 years or older who have an independent clinical risk factor for fracture (see section 1.5) or an indicator of low BMD (see section 1.6) and who are confirmed to have osteoporosis (that is, a T-score of  $-2.5$  SD or below). In women aged 75 years or older who have two or more independent clinical risk factors for fracture or indicators of low BMD, a DXA

scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

- Women aged 65–69 years who have an independent clinical risk factor for fracture (see section 1.5) and who are confirmed to have osteoporosis (that is, a T-score of  $-2.5$  SD or below).
- Postmenopausal women younger than 65 years who have an independent clinical risk factor for fracture (see section 1.5) and at least one additional indicator of low BMD (see section 1.6) and who are confirmed to have osteoporosis (that is, a T-score of  $-2.5$  SD or below).

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 Risedronate and etidronate are recommended as alternative treatment options for the primary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to comply with the special instructions for the administration of alendronate, or have a contraindication to or are intolerant of alendronate (as defined in section 1.7) **and**
- who also have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.5) as indicated in the following table.

**T-scores (SD) at (or below) which risedronate or etidronate is recommended when alendronate cannot be taken**

Age (years)	Number of independent clinical risk factors for fracture (see section 1.5)		
	0	1	2
65–69	– <sup>a</sup>	–3.5	–3.0
70–74	–3.5	–3.0	–2.5
75 or older	–3.0	–3.0	–2.5

<sup>a</sup> Treatment with risedronate or etidronate is not recommended.

If a woman aged 75 years or older who has two or more independent clinical risk factors for fracture or indicators of low BMD has not previously had her BMD measured, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

In deciding between risedronate and etidronate, clinicians and patients need to balance the overall proven effectiveness profile of the drugs against their tolerability and adverse effects in individual patients.

1.3 Strontium ranelate is recommended as an alternative treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate (as defined in section 1.7) **and**
- who also have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.5) as indicated in the following table.

**T-scores (SD) at (or below) which strontium ranelate is recommended when alendronate and either risedronate or etidronate cannot be taken**

Age (years)	Number of independent clinical risk factors for fracture (section 1.5)		
	0	1	2
65–69	– <sup>a</sup>	–4.5	–4.0
70–74	–4.5	–4.0	–3.5
75 or older	–4.0	–4.0	–3.0

<sup>a</sup> Treatment with strontium ranelate is not recommended.

- 1.4 Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.
- 1.5 For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.
- 1.6 For the purposes of this guidance, indicators of low BMD are low body mass index (defined as less than 22 kg/m<sup>2</sup>), medical conditions such as ankylosing spondylitis, Crohn’s disease, conditions that result in prolonged immobility, and untreated premature menopause<sup>2</sup>.
- 1.7 For the purposes of this guidance, intolerance of alendronate, risedronate or etidronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.
- 1.8 For the purposes of this guidance, primary prevention refers to opportunistic identification, during visits to a healthcare professional

<sup>2</sup> Rheumatoid arthritis is also a medical condition indicative of low BMD.

for any reason, of postmenopausal women who are at risk of osteoporotic fragility fractures and who could benefit from drug treatment. It does not imply a dedicated screening programme.

- 1.9 Women who are currently receiving treatment with one of the drugs covered by this guidance, but for whom treatment would not have been recommended according to sections 1.1 to 1.4, should have the option to continue treatment 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 The World Health Organization (WHO) has established diagnostic criteria for osteoporosis based on the measurement of BMD, expressed as the T-score, which is the number of SD below the mean BMD of young adults at their peak bone mass:
- normal BMD: 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 central (hip and/or spine) DXA scanning can estimate fracture risk.
- 2.5 It is 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 'osteoporotic fragility fracture' in the following text). It is often referred to as a low-trauma fracture; that is, a fracture sustained as the result of a force equivalent to the force of a fall from a height equal to, or less than, that of an ordinary chair. In the absence of fracture, osteoporosis is asymptomatic and often remains undiagnosed. Osteoporotic fragility 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 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 fracture. 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 increased fracture risk. Some of these clinical risk factors are at least partly independent of BMD, and include parental history of hip fracture, alcohol intake of 4 or more units per day, prior fracture, long-term systemic use of corticosteroids (the latter two of which are not covered in this guidance), and rheumatoid arthritis.
- 2.12 Factors that are known to be indicators of low BMD include low body mass index (defined as less than 22 kg/m<sup>2</sup>), and medical conditions such as ankylosing spondylitis, Crohn's disease,

conditions that result in prolonged immobility, and untreated premature menopause.

- 2.13 A full review of the 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' (see [www.nice.org.uk](http://www.nice.org.uk)).

### **3 The technologies**

#### **Bisphosphonates: alendronate, etidronate and 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 that has a UK marketing authorisation as a once-weekly preparation (70 mg) for the treatment of postmenopausal osteoporosis. It also has a marketing authorisation at a daily dose of 10 mg for the treatment of osteoporosis in postmenopausal women to prevent fractures. Non-proprietary alendronate (Teva Pharmaceutical Industries) costs £4.12 for four 70-mg tablets and £8.30 for 28 10-mg tablets (excluding VAT; NHS Drug Tariff, 24 February 2008). At these prices the drug costs for 1 year are £53.56 for once-weekly (70-mg) tablets and £108.20 for daily (10-mg) tablets. Proprietary alendronate (Fosamax; Merck Sharp & Dohme) is priced at £22.80 for four 70-mg tablets and £23.12 for 28 10-mg tablets (excluding VAT; 'British national formulary' [BNF] edition 54). At these prices, the drug costs for 1 year are £296.40 for once-weekly (70-mg) tablets and £301.39 for daily (10-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 that has a UK marketing authorisation for the treatment of osteoporosis. The drug is administered in 90-day cycles, with each cycle consisting of etidronate (400 mg/day) for 14 days followed by calcium carbonate (1.25 g/day) for the remaining 76 days. The price per 90-day pack is £21.12 (excluding VAT; BNF 54), 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 that has a UK marketing authorisation 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 28 5-mg tablets and £20.30 for four 35-mg tablets (excluding VAT; BNF 54), which equates to yearly costs of £248.98 for the daily treatment or £264.63 for the 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 should 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 modulator: raloxifene**

- 3.7 Selective oestrogen receptor modulators (SERMs) are 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 & Company) is the only SERM that has a UK marketing authorisation for the treatment of osteoporosis in postmenopausal women. The recommended dosage is 60 mg/day. The prices of 28- and 84-tablet packs are £17.06 and £59.59, respectively (excluding VAT; BNF 54), which equate 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, unexplained 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 or prevention until treatment of the breast cancer, including adjuvant treatment, 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 has a UK marketing authorisation 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 54), 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 summary of product characteristics states that strontium ranelate is not recommended in patients with severe renal impairment and that it 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, drug interactions 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*

### Efficacy

- 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 in which fracture or health-related quality of life was an endpoint and where one of the five 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 used 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 remained constant at all ages, although little evidence was available for the effectiveness of the drugs in women aged 80 years or 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 fractures were sometimes provided, whereas some studies only presented data for all non-vertebral fractures grouped together.

*Alendronate*

- 4.1.5 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, from either dietary intake or calcium supplementation.
- 4.1.6 Two studies, one comparing alendronate with oestrogen alone or with oestrogen and alendronate combined, and the other comparing alendronate with teriparatide (which has a marketing authorisation only for secondary and not primary prevention), found no statistically significant differences between the groups in numbers of 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%,  $p = 0.012$ ).
- 4.1.7 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.
- 4.1.8 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).

- 4.1.9 A post-hoc analysis of data from the largest study on alendronate, the 'Fracture intervention trial' (FIT) RCT (non-vertebral fracture population), suggested that alendronate may be less effective at reducing fractures in women with T-scores above (that is, better than)  $-2.5$  SD than in women with osteoporosis. These results were not statistically significant.
- 4.1.10 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 on 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.
- 4.1.11 Prescription-event monitoring studies in patients for whom alendronate was prescribed (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.

- 4.1.12 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.

#### *Etidronate*

- 4.1.13 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 that currently has a UK marketing authorisation (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.
- 4.1.14 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.
- 4.1.15 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 was 0.81 (95% CI 0.58 to 1.14).

- 4.1.16 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 specialists and patient experts suggested that etidronate may be associated with fewer gastrointestinal adverse effects than other bisphosphonates.
- 4.1.17 The systematic review carried out by the SchARR in 2006 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.

#### *Risedronate*

- 4.1.18 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 outcomes.
- 4.1.19 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).

- 4.1.20 In all of the studies, rates of gastrointestinal adverse events were similar in the risedronate and placebo groups.
- 4.1.21 Prescription-event monitoring studies in patients for whom risedronate was prescribed (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.

*Alendronate and risedronate: meta-analysis*

- 4.1.22 A meta-analysis of pooled data from the alendronate and risedronate studies, carried out by the 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).

*Raloxifene*

- 4.1.23 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 (the dosage

specified in the UK marketing authorisation for the treatment of postmenopausal osteoporosis) and 120 mg/day. Neither reported on health-related quality of life outcomes. The mean age of women 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 below, 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.

- 4.1.24 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).
- 4.1.25 The most serious adverse effect associated with raloxifene was 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, but there is evidence that it lowers serum concentrations of fibrinogen as well as both total and low-density lipoprotein (LDL) cholesterol levels (that is, serum concentrations) without increasing high-density lipoprotein (HDL) cholesterol.

- 4.1.26 The MORE study shows that raloxifene protects against breast cancer, with the RR at 4 years for all types of breast cancer reported as 0.38 (95% CI 0.24 to 0.58), and that for invasive breast cancer as 0.28 (95% CI 0.17 to 0.46).

*Strontium ranelate*

- 4.1.27 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.
- 4.1.28 The Assessment Group reported the results of a published meta-analysis that gave 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). Efficacy in reducing the rate of hip fracture 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).
- 4.1.29 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; nausea, diarrhoea and creatine kinase elevations were the most commonly reported. A serious adverse event associated with strontium ranelate treatment 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.

- 4.1.30 One study published results on health-related quality of life outcomes. 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.

### **Persistence and compliance**

#### *Bisphosphonates*

- 4.1.31 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).
- 4.1.32 A prescription-event monitoring study of patients for whom alendronate was prescribed (n = 11,916) by GPs in England indicated that 24% discontinued treatment within 1 year. In a similar study of patients for whom risedronate was prescribed (n = 11,742) in primary care in England, 30% appeared to have discontinued treatment within 6 months. In another 12 studies reviewed, persistence at 1 year ranged from 16% to 90%.

#### *Raloxifene*

- 4.1.33 Paid claims data from the USA suggested that only 18% of women starting raloxifene treatment continued to take their medication uninterrupted, and an investigation of a pharmacy prescription database indicated that only 44% were continuing treatment at the end of year 2.

#### *Strontium ranelate*

- 4.1.34 Compliance data were reported for two RCTs of strontium ranelate and were similar in the strontium ranelate and placebo arms (ranging from 83% to 93%) at up to 3 years.

### **Acid-suppressive medication and fracture risk**

- 4.1.35 Two cohort and two case–control studies reported on a potential relationship between acid-suppressive medication (proton pump inhibitors or histamine 2 receptor antagonists) and fracture risk. One of the case–control studies, which used the UK General Practice Research Database (GPRD), found that 1 year or more of acid-suppressive medication was associated with an increase in fracture risk. The other case–control study reported a reduction of fracture risk associated with use of histamine 2 receptor antagonists, and that use of other acid-suppressive medication might increase fracture risk. Both studies, however, were unable to demonstrate convincingly that fracture risk was independent of underlying disease that might determine differences in fracture risk.
- 4.1.36 A prospective cohort study excluded women taking medication for fracture prevention and reported an increase in non-vertebral fracture in those taking acid-suppressive medication compared with those who were not. Findings appeared similar for users of proton pump inhibitors or histamine 2 receptor antagonists, but differences in fracture risk were not statistically significant for those using proton pump inhibitors compared with those not using acid-suppressive medication. One large retrospective cohort study using the UK GPRD compared women taking acid-suppressive medication plus bisphosphonates with those taking bisphosphonates alone. This GPRD study reported an increase in fracture risk for some fracture sites with concomitant use of acid-suppressive medication and bisphosphonates, but a reduction in risk for other fracture sites. The information on patients included in this GPRD study was incomplete and details of adjustments for confounders were not reported. The two cohort studies were not fully published, and their analysis may have been prone to confounding.

## 4.2 *Cost effectiveness*

### Manufacturers' models

- 4.2.1 For proprietary alendronate, compared with no treatment, the manufacturer's model provided an incremental cost-effectiveness ratio (ICER) of £8622 per quality-adjusted life year (QALY) gained for 70-year-old women with a T-score below  $-2.5$  SD. The manufacturer's results were more favourable 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's model provided an ICER of £18,634 per QALY gained 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 a prior 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 gained for women aged 74 years. In the second model provided by the manufacturer, which was commissioned from an external body, the ICER was more than £35,000 per QALY gained for all women without a prior osteoporotic fragility fracture and with a T-score of  $-2.5$  SD. However, for women at slightly higher risk of fracture and aged 70 years or older, the corresponding ICER was £13,500 per QALY gained or less. The ICER calculated using the manufacturer's own model was difficult to verify from the information given. The ICERs generated by the second model were more consistent with the

figures provided by the Assessment Group's 2003 model, although they did 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 gained, and were more favourable than the Assessment Group's 2003 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 for 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 a model developed by an external organisation. The ICER was £45,028 per QALY gained for 65-year-old women with a T-score of -2.5 SD and £26,686 per QALY gained for 80-year-old women with a T-score of -2.5 SD. 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 efficacy data for hip fracture 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.

### **The Assessment Group's model**

4.2.6 The Assessment Group provided a cost–utility model with two components (described in detail in the 2005 Strontium Ranelate Assessment Report). As a first step, the model calculated absolute fracture risk from the epidemiological literature on a number of independent clinical risk factors. These data were prepared under the auspices of the WHO and were provided for this appraisal under an academic-in-confidence agreement. As a second step, the model applied RR reductions for fracture taken from the meta-analysis described in section 4.1.22. 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 (see [www.nice.org.uk](http://www.nice.org.uk)), it was assumed that RRs remained constant across all ages, T-scores and fracture status. The most recent analyses carried out by the SchARR were based on the price of non-proprietary alendronate in February 2008 (£53.56 per year for once-weekly 70-mg tablets; £108.20 per year for daily 10-mg tablets).

4.2.7 All osteoporotic fragility fractures in women aged 50 years or 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 also to proximal humerus, rib, sternum, scapula, tibia, fibula and wrist fractures. 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.

- 4.2.8 The model assumed an initial utility in the year of fracture and a higher utility in subsequent years. The time horizon for predicting morbidity was 10 years, consisting of 5 years of treatment with sustained efficacy plus 5 years of linear decline to no effect. However, treatment-related decreases in mortality rate extended beyond the 10-year time horizon. For this, the life expectancy for a woman at the threshold T-score for osteoporosis was calculated from standard life tables, and any increase in mortality rate due to fracture would continue until death or an age of 110 years. In the base case, vertebral-fracture utility was assumed to be lower than hip-fracture utility, and a sensitivity analysis was carried out in which the utility for vertebral fracture was assumed to be the same as that for hip fracture. The percentage of women 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 women with osteoporosis was included. No follow-up BMD scans were included in the model; this reflects current clinical practice in the UK.
- 4.2.9 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 treatment. In addition to the base case, the Assessment Group undertook a number of sensitivity analyses using alternative assumptions, including: persistence with treatment (25% or 75% at 5 years); reduction in the efficacy of the drugs at

reducing the risk of fracture associated with risk factors other than age, prior fracture and low BMD to 0% or 50% (with a consequent upward adjustment of the RR for the risk factors of age, prior 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 do not have such side effects. In base-case analyses for all of the drugs under consideration this was applied to 2.35% of women in the first treatment month and 0.35% of women thereafter and, in sensitivity analyses for bisphosphonates, to 24% of women in the first treatment month and 3.5% of women 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 to this appraisal.

- 4.2.10 For raloxifene, 4-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. The cost effectiveness was modelled excluding the breast cancer benefit, the risk of VTE and the effect on cardiovascular events.
- 4.2.11 The independent clinical risk factors for fracture used in the model were based on the data prepared under the auspices of the WHO (see section 4.2.6) and included body mass index, prior 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 was calculated.

- 4.2.12 The estimates of cost effectiveness were generated for different levels of absolute risk derived from a large number of combinations of T-score (in bands 0.5 SD wide), age and number of independent clinical risk factors for fracture. 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 independent clinical risk factors.
- 4.2.13 As women without fracture do not usually present to clinicians, the Assessment Group also estimated the impact that the costs of identifying women at risk would have 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 who 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 gained approach, but also requires a value of willingness to pay (WTP) for an additional QALY gained. For the calculation of the net benefit of an intervention, the WTP is first multiplied by the incremental QALY gained associated with the intervention, 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.
- 4.2.14 A stepped net-benefit approach was used to estimate, in reverse order, the cost effectiveness of risk assessment, DXA scanning and

treatment of women without a prior fracture. A WTP value of £20,000 per QALY gained was applied in the modelling.

- Step 1. ICERs for treatment versus no treatment were calculated for each intervention for various combinations of age, T-score and number of independent clinical risk factors for fracture (see section 4.2.11). The net benefit of treatment per woman was calculated using the following formula:

Net benefit = (£20,000 × incremental QALYs gained) – incremental costs.

For women for whom the ICER for treatment was more than £20,000 per QALY gained, the net benefit was set to zero.

- Step 2. The net benefit per woman was multiplied by the number of women in the population estimated to fall within each combination of age, T-score and number of independent clinical risk factors for fracture (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 independent clinical risk factors within each age group.
- Step 3. The cost of DXA scanning all of the women in each age/independent clinical risk factor group was subtracted from the net benefit of treatment for that group (calculated as described in step 2). This provides the net benefit of treatment and DXA scanning for the group, assuming that the number of independent clinical risk factors is known. A positive net benefit indicates that DXA scanning of women in that age/independent clinical risk factor group and treating those groups of women in whom the ICER for treatment is £20,000 per QALY gained or less provides an ICER for the entire strategy of less than £20,000 per QALY gained.

- 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/independent 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 £20,000 per QALY gained 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 gained data were presented for each strategy.

*The Assessment Group's model: results for alendronate*

- 4.2.15 First, the Assessment Group calculated ICERs (cost per QALY gained for alendronate compared with no treatment) without identification costs for all combinations of age, T-score and number of independent clinical risk factors for fracture. The cost per QALY gained, compared with no treatment, became more favourable with increasing age and number of independent clinical risk factors, and decreasing T-score (that is, with increasing annual absolute risk of fracture).
- 4.2.16 Then, 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 independent clinical risk factors for fracture) that resulted in an ICER of £20,000 or less (cost per QALY gained compared with no treatment). The analyses shown below 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 prior fracture status set to 50% of that observed for the total

population in the trials (with a consequent upward adjustment of the RR associated with age, BMD and prior 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 and 0.909 in subsequent years (as for hip fracture); 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 £53.56 or £108.20 per year.

4.2.17 For alendronate priced at £53.56 per year (once-weekly treatment), and when assuming that 24% of women in the first treatment month and 3.5% of women thereafter experienced bisphosphonate-related side effects, the model produced the following results:

- A strategy of risk assessment, DXA scanning and treatment with alendronate in women younger than 65 years resulted in an ICER of more than £20,000 per QALY gained.
- A strategy of risk assessment, DXA scanning and treatment with alendronate in women who are confirmed to have osteoporosis (that is, a T-score of  $-2.5$  SD or below) resulted in an ICER of less than £20,000 per QALY gained for all women aged 70 years or older, and for women aged 65–69 years who have an independent clinical risk factor for fracture.

4.2.18 In a sensitivity analysis for alendronate priced at £53.56 per year (with other assumptions as in sections 4.2.16 and 4.2.17), acid-suppressive medication was assumed to affect fracture risk. The data inputs for this were taken from one GPRD study (see section 4.1.35) and represent the midpoint values pooled for patients using acid-suppressive medication. This sensitivity analysis produced the following results:

- A strategy of risk assessment, DXA scanning and treatment with alendronate in women younger than 70 years resulted in an ICER of more than £20,000 per QALY gained.
- A strategy of risk assessment, DXA scanning and treatment with alendronate in women who are confirmed to have osteoporosis (that is, a T-score of  $-2.5$  SD or below) resulted in an ICER of less than £20,000 per QALY gained for all women aged 70 years or older.

The ICER for treatment with alendronate (but excluding identification costs) for a woman aged 70–74 years with a T-score of  $-2.5$  SD (using the assumptions described in sections 4.2.16 and 4.2.17) was £5496 per QALY gained without acid-suppressive medication and £13,236 per QALY gained with acid-suppressive medication. If this woman has an independent clinical risk factor for fracture, the ICERs would be £1567 per QALY gained without and £7727 per QALY gained with acid-suppressive medication.

4.2.19 For alendronate priced at £108.20 per year (daily treatment), and when assuming that 24% of women in the first treatment month and 3.5% of women thereafter experienced bisphosphonate-related side effects, the model produced the following results:

- A strategy of risk assessment, DXA scanning and treatment with alendronate in women younger than 70 years resulted in an ICER of more than £20,000 per QALY gained.
- A strategy of risk assessment, DXA scanning and treatment with alendronate in women who are confirmed to have osteoporosis (that is, a T-score of  $-2.5$  SD or below) resulted in an ICER of less than £20,000 per QALY gained for all women aged 75 years or older and for women aged 70–74 years who have an independent clinical risk factor for fracture. For women aged 70–74 years but with no independent clinical risk factor, the T-score

needs to be  $-3$  SD or below to give an ICER of less than £20,000 per QALY gained.

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

- 4.2.20 Risedronate, raloxifene and strontium ranelate were dominated by alendronate (based on the price of £53.56 per year for alendronate); that is, these three drugs have a higher acquisition cost than alendronate, but are not more efficacious. Analyses were conducted as for alendronate (see section 4.2.16). For risedronate, base-case assumptions for bisphosphonate-related side effects were modelled; that is 2.35% of women in the first treatment month and 0.35% thereafter experienced side effects (see section 4.2.9). In addition a sensitivity analysis was performed, using the assumption that 24% of women in the first treatment month and 3.5% of women thereafter experienced bisphosphonate-related side effects. For raloxifene and strontium ranelate, base-case assumptions for side effects were used. In previous economic modelling and before the most recent price reduction for non-proprietary alendronate, etidronate's cost effectiveness was comparable to that of 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 after the most recent price reduction for alendronate.
- 4.2.21 For risedronate, raloxifene and strontium ranelate, 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, for women aged 65–69 years with an independent clinical risk factor for fracture, the ICERs (without considering costs related to risk assessment and DXA scanning) for risedronate and strontium

ranelate (each compared with no treatment) were more than £45,000 and £90,000 per QALY gained, respectively. For these women, treatment with weekly non-proprietary alendronate, including risk assessment and DXA scanning costs, resulted in an ICER of less than £20,000 per QALY gained.

*The Assessment Group's model: results for other drugs in second-line use*

- 4.2.22 Further analyses were carried out assuming second-line use; that is, costs for risk assessment or DXA scanning were excluded because BMD was assumed to be known from the first-line management.
- 4.2.23 In the economic modelling carried out for this appraisal in 2006, lower ages and higher T-scores resulted in ICERs of less than £20,000 per QALY gained for etidronate compared with risedronate; that is, etidronate was more cost effective than risedronate. Because of the concerns expressed about the weaker clinical evidence base for etidronate, the modelling for this bisphosphonate was not updated.
- 4.2.24 For risedronate in second-line use, when assuming that 2.35% of women in the first treatment month and 0.35% of women thereafter experienced bisphosphonate-related side effects, the model produced the following results:
- Treatment with risedronate in women younger than 65 years resulted in an ICER of more than £20,000 per QALY gained.
  - Treatment with risedronate in women who have the combinations of T-score, age and number of independent clinical risk factors for fracture indicated in the table below resulted in an ICER of less than £20,000 per QALY gained. Including women aged 65–69 years with no independent clinical risk factors for

fracture increased the ICER to more than £20,000 per QALY gained.

**T-scores (SD) at (or below) which risedronate in second-line use resulted in an ICER of less than £20,000 per QALY gained**

Age (years)	Number of independent clinical risk factors for fracture (section 1.5)		
	0	1	2
65–69	– <sup>a</sup>	–3.5	–3.0
70–74	–3.5	–3.0	–2.5
75 or older	–3.0	–3.0	–2.0 <sup>b</sup>

<sup>a</sup> ICER more than £20,000 per QALY gained.

<sup>b</sup> Women with osteopenia are not included in the guidance (see sections 1 and 4.3.6).

4.2.25 For raloxifene, the model produced the following results.

- Treatment with raloxifene in women of any age resulted in an ICER of more than £20,000 per QALY gained.

4.2.26 For strontium ranelate, the model produced the following results.

- Treatment with strontium ranelate in women younger than 65 years resulted in an ICER of more than £20,000 per QALY gained.
- Treatment with strontium ranelate in women who have the combinations of T-score, age and number of independent clinical risk factors for fracture indicated in the table below resulted in an ICER of less than £20,000 per QALY gained. Including women aged 65–69 years with no independent clinical risk factors for fracture increased the ICER to more than £20,000 per QALY gained.

**T-scores (SD) at (or below) which strontium ranelate in second-line use resulted in an ICER of less than £20,000 per QALY gained**

Age (years)	Number of independent clinical risk factors for fracture (section 1.5)		
	0	1	2
65–69	– <sup>a</sup>	–4.5	–4.0
70–74	–4.5	–4.0	–3.5
75 or older	–4.0	–4.0	–3.0

<sup>a</sup> ICER more than £20,000 per QALY gained

4.2.27 If it was assumed that acid-suppressive medication affects fracture risk, the ICER for treatment with risedronate (compared with no treatment, but excluding identification costs) for a woman aged 75 years with a T-score of –3 SD increased from £16,374 to £23,351 per QALY gained (using base-case assumptions about side effects). The corresponding ICER for strontium ranelate was £37,880 per QALY gained compared with no treatment (using base-case assumptions about side effects). For a woman aged 75 years with a T-score of –3.5 SD and one independent clinical risk factor for fracture, the ICER for risedronate increased from £5116 to £10,505 per QALY gained when acid-suppressive medication was assumed to affect fracture risk (using base-case assumptions about side effects). The corresponding ICER for strontium ranelate was £20,935 per QALY gained compared with no treatment (using base-case assumptions about side effects).

### **4.3 Consideration of the evidence**

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of alendronate, etidronate, risedronate, raloxifene and strontium ranelate, having considered evidence on the nature of the condition and the value placed on the benefits of these drugs by women with osteoporosis, those who represent them, and clinical specialists. It also considered the consultation comments received in response to the previous

appraisal consultation documents, the extra analysis undertaken by SchARR in November 2006 and February 2008, and comments received from consultees and commentators after an appeal against an earlier final appraisal determination was upheld in December 2007. It was mindful of the need to take account of the effective use of NHS resources. The Committee was aware of a previous decision of the National Screening Committee not to recommend screening to prevent osteoporotic fracture because of concerns about the accuracy of BMD assessment for the prediction of fracture and because there was no trial evidence indicating that such screening would reduce the incidence of fractures.

4.3.2 The Committee considered the clinical effectiveness data for the bisphosphonates (alendronate, etidronate and risedronate), strontium ranelate and raloxifene. 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 in the degree of certainty that treatment results in a reduction in hip fracture (considered a crucial goal in osteoporosis management). In the case of alendronate and risedronate, the Committee 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.

4.3.3 The Committee noted that strontium ranelate was effective in preventing vertebral and non-vertebral fractures, and the drug 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 had a T-score of  $-2.4$  SD or below.

- 4.3.4 The Committee noted that the evidence for raloxifene showed an effect on risk of vertebral fractures, but did not show an effect on risk of hip fractures. In addition, there was evidence for a beneficial side effect of raloxifene on the incidence of breast cancer.
- 4.3.5 The Committee did not consider it appropriate to make recommendations for the treatment of women on long-term corticosteroid treatment because this patient group is at greatly increased risk of fracture and therefore requires special consideration. The Committee was aware that for women without prior fracture but on corticosteroid treatment, the fracture risk is as high as, or even higher than, the fracture risk for women with a prior fracture. The Appraisal Committee therefore felt that it would be disadvantageous for this group to be included in the current guidance. Recommendations for this group of women will be made within future guidance produced by the Institute.
- 4.3.6 Recommendations for the treatment of women with osteopenia (T-score of between  $-1$  and  $-2.5$  SD below peak BMD) were not made, for two reasons. Firstly, it was agreed after the scope was issued in 2002 that the outcome in this appraisal should be 'the prevention of osteoporotic fractures' and this has been understood by the Committee to be a fragility fracture experienced by women with osteoporosis, not osteopenia. Secondly, not all of the drugs under appraisal have a UK marketing authorisation for treatment of women with osteopenia. Recommendations for this group of women will be made within future guidance produced by the Institute.

**Cost-effectiveness modeling**

- 4.3.7 Because women who have not had a fracture would not normally present to clinicians, the Committee considered it necessary to consider the costs involved in the assessment of fracture risk and of DXA scanning in its appraisal of the drugs for the primary prevention of osteoporotic fragility fractures.
- 4.3.8 The Committee acknowledged the efforts of the Assessment Group to build on the model used previously, particularly in using epidemiological data and a fracture risk algorithm developed under the auspices of the WHO to calculate transition probabilities and to model the identification approaches. The Committee noted that fracture risk is clearly related to age, low BMD and prior fracture. The Committee accepted that most of the independent clinical risk factors for fracture listed in section 4.2.11 are likely to be associated with an increased fracture risk. The Committee was not persuaded that 'current smoking' is a statistically significant risk factor in women, but noted that alcohol consumption of 4 or more units per day is a statistically significant risk factor. However, even for the statistically significant risk factors, 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.
- 4.3.9 With these caveats in mind, the Committee concluded that the Assessment Group's model was a useful basis for exploring the estimates of cost effectiveness; the model used data for a wide age range (age 50–75 years and older) and all osteoporotic fracture sites. Although the Assessment Group's model considered a shorter time period (10 years for predicting morbidity, see section 4.2.8) 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.

- 4.3.10 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 treatment in a proportion of patients. The Committee also noted the effect of the recent price reductions for non-proprietary alendronate (70-mg weekly and 10-mg daily doses) on the cost effectiveness of the drug.
- 4.3.11 The Committee considered the base-case assumptions and those used in additional analyses. The Committee noted that the costs associated with fractures 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.
- 4.3.12 The Committee considered the utility multiplier used in the base-case analysis for the first year after a vertebral fracture and noted that it was based on a hospitalised patient group and not on a typical group of patients with vertebral fractures. Consequently it was considerably lower than the utility value modelled for a hip fracture. Although the Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, it considered that its true value would not greatly outweigh the utility decrement

associated with a hip fracture. Therefore, the Committee 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.

4.3.13 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% was considered both extreme and less plausible. In the analysis accepted by the Committee, the assumption of 50% efficacy of the drugs on fracture risk associated with other risk factors was adjusted by using a correspondingly greater efficacy of the drugs on fractures associated with the key independent clinical risk factors (age, BMD and prior fracture).

4.3.14 The Committee considered the assumptions used in the modelling for the side effects of bisphosphonates, in which 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 in the first treatment month and 0.35% of patients thereafter. Taking into account the persistence data (sections 4.1.31 and 4.1.32) and the comments received from consultees and commentators that about 25–30% of women experience gastrointestinal side effects when first taking a

bisphosphonate, the Committee agreed that it was important to consider the results of a sensitivity analysis assuming that 24% of women were experiencing bisphosphonate-related side effects in the first treatment month and 3.5% of women thereafter.

- 4.3.15 The Committee acknowledged that the modelling of the identification strategies made assumptions necessary about the value of a QALY gained that could be considered an acceptable use of NHS resources. The Committee acknowledged this to be £20,000, as modelled, because there were no additional factors, as referred to in the 'Guide to the methods of technology appraisal' (see [www.nice.org.uk](http://www.nice.org.uk)), that could be considered to increase this value in this situation: that is, in primary prevention where an asymptomatic group of adult patients with a high number needed to treat to avoid a fracture is under consideration.
- 4.3.16 The Committee discussed a number of concerns surrounding other issues that were not represented in the model but which 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 probability that more GP time would be involved in identifying women with risk factors associated with osteoporosis; 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 women 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, for first-

line treatment with a bisphosphonate, these uncertainties could be collectively approximated through the sensitivity analysis for side effects (see section 4.3.14). The Committee was persuaded, however, that the results of the sensitivity analysis need only apply to first-line treatment with a bisphosphonate, because many of the factors that led to the adoption of the sensitivity analysis did not apply for second-line treatment.

### **Alendronate**

4.3.17 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 4.3.8 to 4.3.14). The Committee agreed that, when considering the use of alendronate as a first-line treatment, the sensitivity analysis that captured the uncertainties in the economic model (see section 4.3.14) was the most appropriate. This led the Committee to conclude that alendronate (based on the price of £53.56 per year for once-weekly treatment) would be an appropriate use of NHS resources for the treatment of postmenopausal women who are confirmed to have osteoporosis (that is, a T-score of  $-2.5$  SD or below) who are aged 65 years or older and who have at least one independent clinical risk factor for fracture. The Committee also concluded that, in addition, women aged 70 years and older could be considered for DXA scanning if there was an indication that they might have low BMD, and treated with alendronate if osteoporosis was confirmed. The Committee's reason for restricting DXA scanning for women aged 70 years or older (who visit their GP for any reason) to those with indicators of low BMD was to avoid unnecessarily scanning many women who are well and asymptomatic and who are relatively unlikely to have a low BMD. The Committee was advised by the clinical specialists from the Guideline Development Group for the NICE clinical

guideline on osteoporosis that, in women aged 75 years or older with two or more clinical risk factors, a DXA scan may not be required if the clinician considers it to be clinically inappropriate or unfeasible. This is because a very high proportion of these women would be likely to have a T-score of  $-2.5$  SD or below.

4.3.18 Having reviewed the evidence on independent clinical risk factors for fracture and the views of the clinical specialists, the Committee agreed that the appropriate independent clinical risk factors for fracture are: parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis. The Committee also concluded that there are indicators of low BMD, and these are low body mass index (defined as less than  $22 \text{ kg/m}^2$ ) and medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, and untreated premature menopause. The Committee acknowledged that rheumatoid arthritis is a condition that indicates low BMD, but was also proven to be an independent clinical risk factor for fracture. The Committee noted that prior fracture and long-term systemic corticosteroid use are also relevant clinical risk factors; women with prior fracture or who are on long-term systemic corticosteroid treatment will be considered in NICE technology appraisal guidance on the secondary prevention of osteoporosis and within future guidance produced by the Institute, respectively (see [www.nice.org.uk](http://www.nice.org.uk)).

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

4.3.20 The Committee considered postmenopausal women below the age of 65 years for whom opportunistic identification was not normally cost effective. The Committee recognised that a small number of

postmenopausal women below the age of 65 years who present to healthcare practitioners with conditions that are indicators of low BMD are at high risk of osteoporotic fracture and would not need opportunistic identification. Therefore the Committee concluded that women under 65 years of age with rheumatoid arthritis, ankylosing spondylitis, Crohn's disease or any condition that has resulted in prolonged immobility, provided that they also have an independent clinical risk factor for fracture, should be considered for DXA scanning, and treated with alendronate if osteoporosis is confirmed.

**Considerations for the other drugs under appraisal**

- 4.3.21 The Committee noted that risedronate, etidronate, raloxifene and strontium ranelate were dominated by alendronate (based on the price of £53.56 per year for alendronate); that is, these drugs have a higher acquisition cost than alendronate, but are not more efficacious. The Committee was also aware that, for women for whom weekly non-proprietary alendronate could be recommended based on cost effectiveness, the ICERs for risedronate and strontium ranelate were very high, even without inclusion of identification costs (see examples in section 4.2.21).
- 4.3.22 The Committee considered an approach where the higher costs of risedronate and strontium ranelate were incorporated into the analysis by combining costs based on the estimated use of alendronate, risedronate and strontium ranelate. However, the overall cost effectiveness of such a combined approach for fracture prevention would be less favourable than that of alendronate. As a consequence, some women who would be eligible for treatment with alendronate as recommended in section 1.1 would not be offered treatment using such a combined approach. For this

reason, the Committee did not consider the combined approach to be appropriate.

4.3.23 The Committee considered treatment options available for a woman who is intolerant to alendronate or unable to comply with instructions for administration despite reasonable measures to support continuation of alendronate treatment. The Committee noted that all other treatment options have higher acquisition costs and/or different effectiveness profiles, which would reduce the cost effectiveness of preventive treatment if these drugs were used. The Committee observed that the identification costs associated with finding women who could be cost-effectively treated with one of the other drugs would be negligible, because they would have already undergone an assessment and had a DXA scan in order to be assessed for first-line treatment with alendronate. Therefore, it agreed that the recommendations for this situation should be based on the modelling that excluded identification costs. The Committee also agreed that, when considering second-line or subsequent treatment, the base-case assumptions for side effects could be applied; that is, a 0.91 utility multiplier should be applied to 2.35% of patients in the first treatment month and 0.35% of patients thereafter.

4.3.24 The Committee considered women who cannot take alendronate because of a contraindication or a disability that prevents them from complying with the instructions for administration. Because such a contraindication or disability would be known before the risk assessment, this would comprise a first-line treatment situation, where identification costs are included. Alternative drugs become cost effective at a higher age and lower BMD in a first-line treatment situation, compared with a second-line treatment situation where identification costs are not included. However, such

an approach was considered inappropriate by the Committee because it would unfairly disadvantage women who cannot take alendronate because of a contraindication or a disability. Therefore the Committee concluded that women who cannot take alendronate for these reasons should have access to alternative drugs in the same way as women who cannot tolerate alendronate (that is second-line treatment, where the analysis excluded identification and assessment costs).

*Risedronate*

4.3.25 The Committee concluded that risedronate could be recommended for women who are unable to comply with the special instructions for the administration of alendronate, or have a contraindication to or are intolerant of alendronate, and who have a combination of T-score, age and number of independent clinical risk factors for fracture where treatment with risedronate resulted in an ICER of less than £20,000 per QALY gained without the consideration of identification costs, as outlined in sections 4.2.23–24. The Committee agreed that in women aged 75 years or older, where the T-score needed to make treatment cost-effective was  $-2.5$  SD or below, a DXA scan may not be required if the clinician considers it to be clinically inappropriate or unfeasible (see section 4.3.17).

*Etidronate*

4.3.26 The Committee considered the cost effectiveness of etidronate, and noted that in previous modelling etidronate had a better cost-effectiveness profile than risedronate; since then there has been no change in the evidence base that would affect the relative position of these two drugs. In view of its concerns surrounding the clinical evidence base for etidronate, and taking into account the views of clinical specialists and consultees, the Committee decided that etidronate should not be recommended in preference to

risedronate. However, the Committee agreed that guidance on the use of etidronate should be included in the recommendations, and concluded that etidronate can be recommended as an alternative treatment option for women who cannot take alendronate, as outlined for risedronate in section 4.3.25. In deciding between risedronate and etidronate, clinicians and patients need to balance the overall effectiveness profile of the drugs against their tolerability and adverse effects in individual patients.

*Strontium ranelate*

- 4.3.27 The Committee did not accept the estimate of efficacy for strontium ranelate in preventing hip fracture from the post-hoc subgroup analysis, but it accepted the statistically non-significant RR of 0.85 for hip fracture to acknowledge an effect on this important type of fracture.
- 4.3.28 The Committee concluded that strontium ranelate can be recommended for women who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate, and who have a combination of T-score, age and number of independent clinical risk factors for fracture where treatment with strontium ranelate resulted in an ICER less than £20,000 per QALY gained without the consideration of identification costs, as outlined in section 4.2.26.
- 4.3.29 The Committee agreed a definition of alendronate, risedronate or etidronate intolerance as: persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment with alendronate or risedronate and that occurs even though the instructions for administration have been followed correctly.

*Raloxifene*

4.3.30 The Committee discussed the reported benefits of raloxifene on breast cancer risk, and heard from the clinical specialists that the possibility of preventing vertebral fractures and breast cancer simultaneously could be attractive, particularly to younger postmenopausal women. The Committee also heard from the specialists that evidence on the effect of raloxifene in reducing cardiovascular risk is not considered to be robust and that there is some concern over the increased risk of VTE (see section 4.1.25).

4.3.31 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 fragility fractures. The Committee agreed that, in principle, the side effects of using a drug should be considered; however, 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 treatment for the primary prevention of osteoporotic fragility fractures, as follows:

- From the evidence presented, raloxifene was not as effective as the bisphosphonates for treating osteoporosis.
- Raloxifene's effect on the prevention of breast cancer has not been assessed by the regulatory authorities in the UK.
- 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 could be used for breast cancer prevention.

4.3.32 The Committee noted that treatment with raloxifene did not result in an ICER of less than £20,000 per QALY gained in any age group, even when identification costs were excluded from the modelling.

Therefore, the Committee did not consider raloxifene to be a cost-effective use of NHS resources for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

**Other considerations**

4.3.33 The Committee carefully considered the position of women who cannot take alendronate because of a condition which either makes alendronate contraindicated or which prevents individuals from complying with the instructions for administration for alendronate. In doing so the Committee noted that at least some women in this patient group were likely to be 'disabled' as defined by the Disability Discrimination Act 1995. The Committee was aware of its duties under that Act to avoid unlawful discrimination, to have due regard to the need to promote equality of opportunity for disabled people, and the need to take steps to take account of disabled people's disabilities, as well as its broader legal duties to ensure that its guidance is fair and reasonable.

4.3.34 The Committee noted that the drugs other than alendronate are cost effective only for patients at higher risk of fracture than the risk levels at which alendronate is cost effective. If these other drugs are recommended for use by patients who cannot take alendronate only when those patients meet the criteria at which these alternative drugs become cost effective, these patients will not receive preventative treatment unless they are at higher risk of fracture than the risk levels at which alendronate is recommended. The Committee therefore considered whether, for women who cannot receive alendronate, the other drugs should be recommended at the same risk levels as alendronate (that is using the criteria established as being cost effective for alendronate) in order to provide access to preventative treatment for all patients with the same level of risk. The Committee reviewed the ICERs for

risedronate and strontium ranelate within the criteria established to be cost effective for alendronate. The Committee noted that the prices for risedronate and strontium ranelate are approximately five to six times higher than the price for non-proprietary weekly alendronate, and that the ICERs for these drugs compared with no treatment were very high. For example, the ICER for strontium ranelate for women aged 65–69 years with an independent clinical risk factor for fracture was approximately £90,000 per QALY gained (see section 4.2.21). The Committee noted that strontium ranelate would be the most likely choice to be considered for women who are unable to comply with the instructions for administration of alendronate, because the instructions for administration of alendronate and risedronate are similar. The Committee took the view that recommending drugs other than alendronate using the same criteria as alendronate for women who cannot take alendronate would not be justified in this case because of the very high ICERs for the alternative drugs. In reaching this decision the Committee had regard to the fact that the impact of refusing the more favourable recommendation is that there is no generally recommended preventative treatment for a particular group of patients who are at the lower end of fracture risk for which treatment was considered, but that the alternative drugs are recommended when these patients are at higher risk of fracture.

- 4.3.35 The Committee considered that it is important to maximise the number of patients who are able to take alendronate. Some women will be unable to take alendronate in any circumstances because of contraindication, intolerance or inability to comply with the instructions for administration. However, some women who have a disability that makes it difficult for them to comply with the instructions for administration of alendronate would be able to receive the drug if they received assistance in taking it. The

Committee concluded that all reasonable steps should be taken to provide women who have a disability that makes it difficult for them to comply with the instructions for administration of alendronate, with such practical support and assistance with administration (for example through district nurse visits or other home support services), as will enable them to take the drug.

- 4.3.36 The Committee was aware of the availability of the FRAX internet-based tool, which can be used to calculate a 10-year absolute risk of fracture, developed under the auspices of the WHO. This assessment tool was based on the same epidemiological data that were used in the Assessment Group's model. However, the Committee was not persuaded that recommendations about treatment should be based on absolute risk as calculated using FRAX. Firstly, the Committee did not agree that all clinical risk factors included in the WHO algorithm were appropriate (see sections 4.2.11 and 4.3.8). Secondly, the Committee was aware that absolute fracture risk is not directly related to cost effectiveness, as outlined in the strontium ranelate assessment report issued in 2005. This is because absolute fracture risk is the total for all fracture sites, but different fracture sites have different impacts on quality of life, costs and mortality. Therefore cost effectiveness is dependent on the contribution from each fracture site to the total fracture risk. Thirdly, the Committee had agreed that treatment benefit had not been proven for fracture risk associated with all independent clinical risk factors (section 4.3.8). Therefore, the Committee concluded that using a combination of T-score, age and number of independent clinical risk factors for fracture is more appropriate for defining treatment recommendations in this appraisal.

- 4.3.37 The Committee was made aware of data indicating that acid-suppressive medication leads to a small increase in fracture risk and that co-administration of acid-suppressive medication and bisphosphonates may lead to an increased fracture risk compared with bisphosphonate administration alone. The Committee was not persuaded by this evidence; it noted that the data are observational and have not been reported in full, and are different for different fracture sites and for different acid suppressors. Furthermore, the Committee was informed, during consultation, of analyses showing that acid-suppressive medication given in addition to risedronate did not increase fracture risk. However, the Committee concluded that caution should be exercised when considering the evidence about co-prescription of acid-suppressive medication and bisphosphonates.
- 4.3.38 The Committee noted sensitivity analyses that included the assumption of an increase in fracture risk for women for whom acid-suppressive medications are co-prescribed (see section 4.2.18). The analysis for treatment strategies did not decrease the T-scores at which the ICERs for alendronate fell below £20,000 to the T-scores established for strategies including strontium ranelate. The Committee also noted that the ICERs for treatment compared with no treatment for an individual woman with a relevant combination of age and T-score were not more favourable for strontium ranelate than for risedronate even if an effect of acid-suppressive medication was assumed. The Committee considered that the evidence for this effect was not sufficiently robust. However, it concluded that the relative positions of alendronate, risedronate and strontium ranelate would remain unchanged even if an effect of acid-suppressive medication was assumed (see section 4.3.34). The Committee therefore concluded that it was not

necessary to change its recommendations (section 1) to take account of acid-suppressive medication.

### **Calcium and vitamin D prerequisites for treatment**

4.3.39 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 unless clinicians are confident that women who receive treatment for osteoporosis have an adequate calcium intake and are vitamin D replete. The Committee suggested that the forthcoming NICE clinical guideline on osteoporosis could specify how such assessments should be made and what supplementation should be prescribed (see [www.nice.org.uk](http://www.nice.org.uk)).

## **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 that 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](http://www.nice.org.uk/TAXXX)) [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit support for monitoring local practice.

## 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.

## 7 Related NICE guidance

### Published

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 (2005). Available from: [www.nice.org.uk/TA087](http://www.nice.org.uk/TA087)

### Under development

NICE is developing the following guidance (details available from [www.nice.org.uk](http://www.nice.org.uk)):

- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal guidance (publication date to be confirmed).
- Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. NICE clinical guideline (publication date to be confirmed).

## 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 these technologies will be considered for review in July 2010.

Andrew Stevens  
Chair, Appraisal Committee  
June 2008

## **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 (2006–2008)**

Professor of Medical Statistics, University of Leicester

#### **Ms Julie Acred (2004–2005)**

Chief Executive, Derby Hospitals NHS Foundation Trust

#### **Dr Ray Armstrong (2008)**

Consultant Rheumatologist, Southampton General Hospital

#### **Dr Jeff Aronson (2006–2008)**

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

#### **Dr Darren Ashcroft (2004–2008)**

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

**Professor David Barnett (2004–2008)**

Professor of Clinical Pharmacology, University of Leicester

**Dr Peter Barry (2004–2008)**

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

**Professor Stirling Bryan (2006–2008)**

Head, Department of Health Economics, University of Birmingham

**Mr Brian Buckley (2004–2006)**

Vice Chairman, InContact

**Professor John Cairns (2006–2008)**

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 (2004–2008)**

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 (2004–2008)**

Health Economist, London School of Hygiene and Tropical Medicine

**Professor Trisha Greenhalgh (2004–2005)**

Professor of Primary Health Care, University College London

**Lynn Field (2006–2008)**

Nurse Director, Pan Birmingham Cancer Network

**Professor Gary A Ford (2004–2005)**

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

National Institute for Health and Clinical Excellence

**Professor Christopher Fowler (2006–2008)**

Professor of Surgical Education, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London

**Dr Fergus Gleeson (2004–2008)**

Consultant Radiologist, Churchill Hospital, Oxford

**Ms Sally Gooch (2004–2008)**

Independent Nursing and Healthcare Consultant

**Mrs Barbara Greggains (2006–2008)**

Lay member

**Mr Sanjay Gupta (2005–2008)**

Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

**Ms Linda Hands (2004–2005)**

Consultant Vascular Surgeon, John Radcliffe Hospital, Oxford

**Professor Philip Home (2005–2006)**

Professor of Diabetes Medicine, University of Newcastle upon Tyne

**Dr Peter Jackson (2005–2006)**

Clinical Pharmacologist, University of Sheffield

**Professor Peter Jones (2004–2006)**

Professor of Statistics and 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 Adviser to the Department of Health

**Mr Terence Lewis (2006–2008)**

Lay member

**Dr George Levvy (2005–2006)**

Lay member

**Professor Gary McVeigh (2006–2008)**

Professor of Cardiovascular Medicine, Queens University, Belfast

**Professor Jonathan Michaels (2004–2006)**

Professor of Vascular Surgery, University of Sheffield

**Dr Ruairidh Milne (2004–2008)**

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology, University of Southampton

**Dr Neil Milner (2004–2008)**

General Practitioner, Tramways Medical Centre, Sheffield

**Dr Rubin Minhas (2004–2008)**

General Practitioner, CHD Clinical Lead, Medway PCT

**Dr John Pounsford (2006–2008)**

Consultant Physician, Frenchay Hospital, Bristol

**Dr Rosalind Ramsay (2006–2008)**

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital, London

**Dr Christa Roberts (2006–2008)**

UK Country Manager, Abbott Vascular

**Dr Stephen Saltissi (2006–2008)**

Consultant Cardiologist, Royal Liverpool University Hospital

**Mr Miles Scott (2004–2006)**

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

**Dr Lindsay Smith (2005–2008)**

General Practitioner, East Somerset Research Consortium

**Mr Roderick Smith (2006–2008)**

Finance Director, West Kent PCT

**Mr Cliff Snelling (2006–2008)**

Lay member

**Mr Malcolm Stamp (2004)**

Chief Executive, Addenbrooke's NHS Trust

**Professor Ken Stein (2004–2008)**

Professor of Public Health, Peninsula College of Medicine and Dentistry, University of Exeter

**Professor Andrew Stevens (Chair) (2004–2008)**

Professor of Public Health, University of Birmingham

**Dr Rod Taylor (2006–2008)**

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 Appraisal Committee meetings to observe and to contribute as advisers to the Committee.

- Professor Cameron G Swift (2008), King's College London School of Medicine Clinical Age Research Unit King's College Hospital, London
- Dr Maggie Westby (2008), Senior Research and Development Fellow, National Collaborating Centre for Nursing and Supportive Care
- Professor Juliet Compston (2005–2007), Professor of Bone Medicine, University of Cambridge School of Clinical Medicine and Addenbrooke's NHS Trust
- Dr Peter Selby (2005–2007), Consultant Physician, Central Manchester and Manchester Children's University Hospitals NHS Trust

- Professor David Barlow (2005–2007), 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.

**Dr Ruaraidh Hill, Prashanth Kandaswamy and Emma Pugh**

Technical Leads

**Zoe Charles and Dr Elisabeth George**

Technical Advisers

**Natalie Bemrose**

Project Manager

## Appendix B: Sources of evidence considered by the Committee

A Extra analysis reports were prepared by the Decision Support Unit, the School of Health and Related Research, University of Sheffield (ScHARR).

- Stevenson M, Analyses of cost-effective BMD scanning and treatment strategies for generic alendronate, and the cost-effectiveness of risedronate and strontium ranelate in those people who would be treated with generic alendronate, February 2008.
- Lloyd Jones M, Critique of evidence put forward by Servier suggesting an association between acid-suppressive medication and fracture risk, February 2008.

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

- Stevenson M, Analyses of cost-effective BMD scanning and treatment strategies for generic alendronate, and the cost-effectiveness of risedronate and strontium ranelate in those people who would be treated with generic alendronate. February 2008.
- Lloyd Jones M, Critique of evidence put forward by Servier suggesting an association between acid-suppressive medication and fracture risk. February 2008.
- Stevenson M, Analyses of cost-effective BMD scanning and treatment strategies for generic alendronate, risedronate, strontium ranelate, raloxifene and teriparatide following corrections to the methodology associated with lower efficacy in some risk factors, November 2006.
- Stevenson M, Davis S, Addendum to the Assessment Report: Analyses of the cost-effectiveness of pooled alendronate and risedronate, compared with strontium ranelate, raloxifene, etidronate and teriparatide, September 2006.
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- Lloyd Jones M and Wilkinson A, Adverse effects and persistence with therapy in patients taking oral alendronate, etidronate or risedronate: systematic reviews, July 2006.

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- Stevenson M and Davis S, Addendum to the Assessment Report: Analyses of the cost-effectiveness of pooled alendronate and risedronate, compared with strontium ranelate, raloxifene, etidronate and teriparatide, July 2005.
- Stevenson M, Lloyd Jones M, de Nigris E et al, The clinical effectiveness and cost effectiveness of prevention and treatment of osteoporosis, December 2003.

C 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
- Merck Sharp & Dohme
- Proctor & Gamble Pharmaceuticals
- Servier
- 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 (did not provide written evidence and without the right of appeal):

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

D The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They provided oral evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women by attending the initial Committee discussion and/or providing written evidence to the Committee.

- Mrs Jackie Parrington, Deputy Chief Executive, National Osteoporosis Society, nominated by the National Osteoporosis Society – patient expert
- Mrs Anthea Franks, nominated by the National Osteoporosis Society – patient expert
- Professor Juliet Compston, Professor of Bone Medicine, University of Cambridge School of Clinical Medicine and Addenbrooke's NHS Trust, nominated by the Royal College of Physicians – clinical specialist
- Dr RM Francis, Reader in Medicine (Geriatrics) and Honorary Consultant Physician, British Geriatrics Society, nominated by

the British Geriatrics Society and the National Osteoporosis Society – clinical specialist

- Dr Caje Moniz, Consultant and Clinical Director, King's Healthcare NHS Trust, nominated by the National Osteoporosis Society – clinical specialist
- Dr Peter Selby, Consultant Physician, Central Manchester and Manchester Children's University Hospitals NHS Trust, nominated by the Society of Endocrinology and the National Osteoporosis Society – clinical specialist