NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Denosumab for the prevention of osteoporotic fractures in postmenopausal women

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group's report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide clarification on:

- **clinical effectiveness data**
- **probabilities and model calculations**
- **the utility multipliers applied**
- **cost assumptions.**

The manufacturer was also asked to provide the following:

- **ICERs by bands of both age and T-score (that is, number of standard deviations (SD) from the mean BMD of young, healthy adults of the same gender at their peak bone mass)**
- **subgroup analysis for patients with none, one, and two or more independent clinical risk factors (within each subgroup defined by age and T-score) for all relevant comparators.**

The manufacturer originally provided a submission of 468 pages. NICE requested that a more concise submission be provided because the exceptional length of the original submission would lead to difficulties in the course of the appraisal. The manufacturer provided a shorter, restructured submission, but pointed out several factors that necessitated the length of the original comprehensive evidence submission. The most notable factors were the number of comparators included in the final scope, the complexity of existing NICE guidance on osteoporosis (technology appraisal [TA] guidance 160 and 161) and the unusually high volume of data for denosumab available at time of launch.

Indicative licensed indication

The anticipated licensed indication for denosumab (Prolia, Amgen) is as follows:

Denosumab is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fractures. Denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

The European Medicines Agency (EMEA) issued a positive opinion for this indication in December 2009.

Key issues for consideration

- What is the Committee's view on the relevant comparators for denosumab?
- What is the Committee's view on the methodology of the indirect comparison carried out by the manufacturer?
- What is the Committee's view on whether denosumab should be given in primary care rather than in secondary care?
- If denosumab was given in primary care, what is the Committee's view on its provision as part of general medical services, and should denosumab be regarded as an enhanced service requiring negotiation of an additional payment?
- What is the Committee's view on the administration and monitoring costs used for denosumab in the economic analysis?
- The manufacturer's model assumes that people who had a vertebral fracture could not then have a wrist fracture or other type of osteoporotic fracture (other than a subsequent vertebral fracture or hip fracture), and that those who had a hip fracture could only have further hip fractures. Does the Committee think that this assumption is appropriate?
- The economic model assumes that osteoporosis treatment is stopped after 5 years. Does the Committee consider that this assumption is appropriate?
- The economic model assumes that the utility loss relative to population norms remains at a constant rate in the second and subsequent years after

hip fractures or vertebral fractures. Does the Committee think that this assumption is appropriate?

- The model assumes that the effect of treatment for osteoporosis lasts for 1 year after the drug is stopped. What is the Committee's view on this assumption? Is it appropriate for denosumab?
- Reduction in risk of breast cancer due to osteoporosis treatment has not been included in the economic model. What is the Committee's view on whether this factor should be included?
- Does the Committee feel that all adverse events associated with denosumab (short-term and long-term) have been captured appropriately in the economic analysis? What is the Committee's view on the lack of long-term safety data?
- What is the Committee's view on the subgroup analyses and the cost effectiveness estimates across T-score bands?

Related NICE appraisals

Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal 161 (2008; amended January 2010). Available from www.nice.org.uk/guidance/TA161

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE technology appraisal 160 (2008; amended January 2010). Available from www.nice.org.uk/guidance/TA160

Appendix B lists the recommendations for these appraisals.

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

The recommendations in 'Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the **primary** prevention of osteoporotic fragility fractures in postmenopausal women' (NICE technology appraisal guidance 160) include:

- Whether or not a postmenopausal woman with osteoporosis is offered one of these drugs to prevent bone fractures depends on her age, her bone mineral density (BMD), and how many risk factors for fracture and indicators of fragile bones she has.
- Alendronate is recommended as a possible treatment for preventing bone fractures in postmenopausal women with osteoporosis but who have not had a fracture.
- If a woman cannot take alendronate, then risedronate and etidronate are recommended under certain circumstances as possible alternatives.
- If a woman cannot take oral bisphosphonates (alendronate and either risedronate or etidronate), then strontium ranelate is recommended under certain circumstances as a possible alternative.
- Raloxifene is not recommended as a treatment option.

The recommendations in 'Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the **secondary** prevention of osteoporotic fragility fractures in postmenopausal women' include:

- Whether or not a postmenopausal woman who has had a bone fracture because of osteoporosis is offered treatment to prevent further fractures will depend on her age, her BMD and how many risk factors for fracture she has.

- Alendronate is recommended as a possible treatment for preventing bone fractures in postmenopausal women who have already had a fracture and have had osteoporosis diagnosed.
- If a woman cannot take alendronate, then risedronate and etidronate are recommended under certain circumstances as possible alternative treatments to prevent further fractures.
- If a woman cannot take alendronate and either risedronate or etidronate, then strontium ranelate and raloxifene are recommended under certain circumstances as possible alternatives.
- If a woman cannot take alendronate, and either risedronate or etidronate, and strontium ranelate, teriparatide is recommended under certain circumstances as a possible alternative. Teriparatide is also recommended as a possible alternative treatment for a woman who has another fracture when she has been taking alendronate, risedronate or etidronate for 1 year and her bone density has declined.

Population	Postmenopausal women at risk of osteoporotic fragility fracture
Intervention	Denosumab 60 mg every 6 months
Comparators	Primary comparators: strontium ranelate, raloxifene and no treatment (placebo). Secondary comparators: teriparatide, intravenous ibandronate and zoledronate. Supplementary comparators: alendronate, risedronate, etidronate and oral ibandronate are included in the manufacturer's submission appendices for completeness (section 9.15).
Outcomes	The outcome measures considered include: osteoporotic fragility fracture, bone mineral density (BMD), mortality, health-related quality of life and adverse effects of treatment.
Economic evaluation	The cost effectiveness of denosumab is expressed in terms of incremental cost per quality-adjusted life year (QALY). The time horizon for estimating clinical and cost effectiveness is patients' lifetimes to reflect any differences in costs or outcomes between the technologies. Costs are considered from the perspective of the NHS and of personal and social services.
Other considerations	The submission is in accordance with the marketing authorisation. The economic analysis explores alternative scenarios for underlying risk of fracture. Two approaches are explored for fracture risk in the economic analysis. Absolute risk is estimated from published epidemiological data. In a scenario analysis, fracture risk is estimated using the World Health Organization's (WHO) fracture risk assessment tool (FRAX) for previously untreated patients. Assessment of the probability of fracture is performed in the model based on the estimates of underlying absolute risk and relative risk estimated via systematic review and meta-analysis. Continuation of treatment is in line with previous NICE technology assessments in osteoporosis. The cost of fracture risk assessment for all osteoporosis therapies is assumed to consist of a once yearly visit to a general practitioner (GP) and a BMD measurement once every second year.

1.2 Evidence Review Group comments

1.2.1 Population

The Evidence Review Group stated that the population defined in the manufacturer's decision problem (postmenopausal women with osteoporosis as defined by the World Health Organisation [WHO]) was consistent with the population defined in the final scope.

1.2.2 Intervention

Denosumab is a monoclonal antibody that reduces osteoclast activity and hence reduces bone breakdown, and is the first drug of its class. According to the manufacturer's submission, a 60 mg dose is administered by subcutaneous injection into the thigh, abdomen or back of arm every 6 months.

1.2.3 Comparators

The manufacturer's submission stated that denosumab is expected to be approved as a treatment option for postmenopausal women diagnosed with osteoporosis, for whom oral bisphosphonates are unsuitable (reasons for unsuitability include: inability to comply with special instructions for administration; a contraindication; or intolerance). The manufacturer selected strontium ranelate, raloxifene and no treatment as the primary comparators in their submission. Ibandronate (intravenous), zoledronate, and teriparatide were considered to be secondary comparators. Supplementary comparisons with oral bisphosphonates were also provided in the appendices to the manufacturer's submission.

The Evidence Review Group noted that the primary comparators selected were consistent with the recommendations in TA160 and TA161, and although theoretically teriparatide should be included as a primary comparator its use is restricted by TA160 and TA161 and, therefore, its inclusion as a secondary comparator was appropriate. The group expressed concern that

because TA160 and TA161 did not include zoledronate and ibandronate, the manufacturer dismissed these technologies as not standard care and regarded them as secondary comparators. The group quoted clinical opinion suggesting that both zoledronate and ibandronate (oral and intravenous) are used in UK clinical practice. The group expressed the view that zoledronate and ibandronate should have been considered as primary comparators in people who cannot take oral bisphosphonates because zolendronate and ibandronate may be more convenient for some people and have similar effectiveness to oral bisphosphonates.

1.2.4 Outcomes

The Evidence Review Group noted that all outcomes defined in the final scope were addressed in the manufacturer's submission. These included osteoporotic fragility fractures, BMD, mortality, health-related quality of life, adverse effects of treatment. The group expressed some doubt about the value of bone mineral density as an outcome (in terms of health-related quality of life), and believed that the key outcome was fracture. The group stated that the manufacturer's submission also gave appropriate attention to adherence, persistence, and compliance with data from the General Practice Research Database.

1.2.5 Economic evaluation

The Evidence Review Group noted that the manufacturer's submission appropriately used the incremental cost per quality-adjusted life-year (QALY) gained as a measure of cost effectiveness, in accordance with the NICE reference case. Costs were appropriately considered from the perspective of the NHS and of personal and social services.

1.2.6 Timeframe

The manufacturer's decision problem defined the timeframe as a lifetime horizon, and stated that timeframe of death or the age of 100 years was

chosen because it was consistent with evidence on morbidity and mortality associated with major osteoporotic fractures.

1.3 Statements from professional/patient groups and nominated experts

Professional groups stated that in UK clinical practice varies in the assessment and treatment of osteoporosis in postmenopausal women for both primary and secondary prevention. Treatment is usually oral bisphosphonates; the most commonly used is alendronate, but risedronate and ibandronate are also used. Alternatively, intravenous bisphosphonates such as zoledronate (given annually) or ibandronate (given every 3 months) are used in people who are unable to take, tolerate, or absorb oral treatment. Intravenous bisphosphonates are also used if people have poor compliance and persistence with daily or weekly medication, or do not respond to oral bisphosphonates. The clinical specialists stated that strontium ranelate is used in patients who are unable to take or tolerate bisphosphonates or who do not respond to other treatments. Teriparatide is generally used only in patients with severe osteoporosis who do not respond to other treatments. The clinical specialists noted that the alternatives to denosumab are oral and intravenous bisphosphonates and strontium ranelate.

- The professional and patient's groups stated that because denosumab is a new biological agent, its use would probably be restricted to people with severe osteoporosis who are at high risk of fragility fractures and are either unable to take or to tolerate bisphosphonates such as:
- those with vertebral fractures, incapacitation, or disabilities who are unable to remain upright for 30 minutes
- those with mental illness or memory problems
- those with renal impairment or gastrointestinal problems.

The professional and patient's groups noted that administration of denosumab by subcutaneous injection twice yearly may be more convenient than oral

treatment for some people because it would not affect their daily life and may result in improved compliance and persistence, and avoid the problems with absorption of oral treatments. However, the groups noted that the method of administration could also be a disadvantage to some people who are not comfortable with injections, and that both injections and denosumab itself might be associated with increased risk of infection.

Professional groups noted that treatment with denosumab would probably be initiated in a specialist clinic in secondary care. Subsequently, treatment could be administered by doctors or nurses in primary care in a shared-care arrangement or by self-administration. Professional groups believed that limited training will be necessary to teach the patient, carer, nurse or practitioner how to give the treatment safely and effectively, but wider education in primary care would be needed for shared-care arrangements to be implemented. Facilities to ensure adequate response to therapy would be needed including assessment of ongoing response using biochemical tests (to ensure adequate calcium and vitamin D status and decreases in markers of bone resorption).

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's submission presented clinical effectiveness data from one main randomised clinical trial. The fracture reduction evaluation of denosumab in osteoporosis every 6 months (FREEDOM) study, was a multicentre, double-blind, placebo-controlled trial that enrolled 7868 postmenopausal women aged between 60 and 90 years with bone mineral density T-score (that is, the number of standard deviations (SD) from the mean BMD of young, healthy adults of the same gender at their peak bone mass) of less than −2.5 to equal or greater than −4.0). Patients were randomly assigned to a

subcutaneous injection of either 60 mg denosumab or placebo twice yearly for 3 years. All participants also took daily calcium and vitamin D supplements

The primary outcome was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture, and tertiary outcomes included other fracture endpoints (see page 76 of the manufacturer's submission). Health-related quality of life was assessed in terms of change from baseline in patient-reported outcomes using the osteoporosis assessment questionnaire-short version (OPAQ-SV) physical function, emotional status, back pain score, and EUROQOL-5D (EQ5D) questionnaire.

Several supporting studies that examined bone mineral density as the primary outcome were presented in the appendices to the manufacturer's submission.

Results of the FREEDOM study

Results of the FREEDOM study demonstrated that the 36-month incidence of new radiographically diagnosed vertebral fractures was 2.3% (86 of 3702 patients) in the denosumab group and 7.2% (264 of 3691 patients) in the placebo group, representing a 68% reduction in relative risk ($p < 0.001$). The reduction in risk was similar during each year of the trial. Similar reductions were seen for clinically diagnosed vertebral fracture (69%) and multiple new radiographically diagnosed vertebral fractures (61%; $p < 0.001$ for both comparisons). The results of the FREEDOM study are summarised in Table 1.

Table 1 Fracture endpoint results from FREEDOM at 36 months as presented in the manufacturer's submission[a]

Outcome	Number of people receiving denosumab	Number of people recieving placebo	Difference in rates (95% CI)	Relative risk or hazard ratio (95% CI)[b]	p value
Primary endpoint					
New radiographically diagnosed vertebral fracture	86 (2.3%)	264 (7.2%)	4.8 (3.9 to 5.8)	0.32 (0.26 to 0.41)	<0.001
Secondary endpoints					
Non-vertebral fracture[c]	238 (6.55%)	293 (8.0%)	1.5 (0.3 to 2.7)	0.80 (0.67 to 0.95)	0.01
Hip fracture	26 (0.7%)	43 (1.2%)	0.3 (−0.1 to 0.7)	0.60 (0.37 to 0.97)	0.04
Other fracture endpoints					
New clinically diagnosed vertebral fracture	29 (0.8%)	92 (2.6%)	1.7 (1.1 to 2.3)	0.31 (0.20 to 0.47)	<0.001
Multiple (≥ 2) new vertebral fractures	23 (0.6%)	59 (1.6%)	1.0 (0.5 to 1.5)	0.39 (0.24 to 0.63)	< 0.001

The numerical differences in the rates for denosumab and placebo are not equal to the presented differences in column 3 for new radiographic vertebral fractures and hip fractures because they are based on the Cox proportional hazards model stratified by age stratification variable (Cummings et al. 2009).

CI=confidence interval.

[a] The percentages of new and multiple new radiographically diagnosed vertebral fractures are calculated for 3,702 people in the denosumab group and 3,691 in the placebo group who underwent radiography of the spine at baseline and during at least one later visit. The proportion of non-vertebral, hip and new clinical vertebral fractures are cumulative Kaplan–Meier estimates for 3,902 people in the denosumab group and 3,906 in the placebo group.

[b] Relative risks are based on the Chochran–Mantel–Haenszel method with adjustment for the age-stratification variable for vertebral fractures. Hazard ratios are based on the Cox proportional hazards model with adjustment for the age-stratification variable for non-vertebral, hip and clinical vertebral fractures.

[c] A total of 28 people (13 in the denosumab group and 15 in the placebo group) had non-vertebral fractures associated with severe trauma and were not included in the analysis.

Ten-year fracture risks for major osteoporotic fracture and hip fracture were estimated for the population in the FREEDOM study using the FRAX algorithms and demonstrated that denosumab reduced the incidence of new radiographically diagnosed vertebral, non-vertebral and hip fractures across subjects with a wide range of baseline 10-year fracture risks. No statistically significant interaction was seen between treatment and 10-year fracture risks for any of the fracture endpoints; that is, there is no relationship between the efficacy of denosumab and fracture risk. After controlling for the 10-year probability of major osteoporotic fracture, the treatment effect of denosumab on the incidence of new radiographically diagnosed vertebral fracture remained statistically significant (odds ratio [OR] 0.31, 95% confidence interval [CI] 0.24 to 0.39, $p < 0.0001$), as was the time to first non-vertebral fracture (hazard ratio [HR] 0.80 [0.67 to 0.95], $p = 0.0108$). Furthermore, after controlling for 10-year probability of hip fracture, the treatment effect of denosumab remained statistically significant for time to first hip fracture (HR 0.60 [0.37 to 0.97], $p = 0.0355$).

Health-related quality of life was assessed by the OPAQ-SV and EQ-5D questionnaire at baseline and every 6 months for 3 years. Among patients who completed the study, completion rates for measures of health-related quality of life at year 3 were 83% for OPAQ-SV and 82% for EQ-5D. No significant differences were seen between treatment groups in measures of health-related quality of life at baseline compared with year 3, or in comparing women without any fractures with those with incident clinical fractures. Decreases in two OPAQ-SV dimensions (physical function and emotional status) and in EQ-5D health index and visual analogue scale scores (all $p < 0.001$) were reported at year 3 regardless of treatment group. Changes from baseline to year 3 for each OPAQ-SV dimension and EQ-5D scores were positively correlated (all $p < 0.0001$). Results from assessments of health-related quality of life are summarised in Table 2.

Table 2 Changes from baseline to year 3 in OPAQ-SV and EQ-5D scores in the FREEDOM study[a]

OPAQ-SV dimension/ EQ-5D scores	Patients with incident clinical fractures[b] (n = 670)		Patients with no incident fractures (n = 6,821)	
	n	Mean (95% CI)	n	Mean (95% CI)
OPAQ-SV: physical function	567	–4.1 (–5.7 to –2.6)*	5585	–0.5 (–0.9 to –0.1)
OPAQ-SV: emotional status	566	–5.0 (–6.6 to –3.5)*	5588	–0.8 (–1.2 to –0.4)
OPAQ-SV: back pain	567	1.6 (–0.4 to 3.7)*	5597	4.6 (4.0 to 5.2)
EQ-5D: health index score	562	–0.02 (–0.04 to 0.00)**	5535	0.01 (0.01 to 0.02)
EQ-5D: visual analogue scale score	564	–2.2 (–3.8 to –0.6)**	5576	–0.1 (–0.5 to 0.4)

CI = confidence interval; EQ-5D = EuroQol-5D; OPAQ-SV = Osteoporosis Assessment Questionnaire–Short Version.

*p ≤ 0.0001, **p < 0.001 compared with the group with no incident fractures; based on an analysis of covariance model adjusting for age and the respective baseline score.

[a] People with only morphometric (that is, a change in the form [size and shape]) vertebral fractures were not included in the analysis.

[b] Includes all people with clinical fractures regardless of trauma severity (excluding skull, facial, finger and toe fractures).

Source: Siris et al. 2009b.

The manufacturer presented a range of subgroup analyses for the following: age, [redacted], geographical region, race, body-mass index (post-hoc analysis), calculated creatinine clearance, prior use of osteoporosis medications, femoral neck T-score (post-hoc analysis), [redacted], prevalent vertebral fracture, prior non-vertebral fracture at age ≥ 55 years, fracture risk based on age, BMD and prevalent vertebral fracture, [redacted]. For the results of these analyses please refer to tables B12 to B14 on pages 91–94 of the manufacturer's submission.

Only one serious adverse effect of denosumab was reported in the FREEDOM study. A statistically significant difference was noted in skin infections, which occurred in 12 patients receiving denosumab compared with one patient receiving placebo ($p = 0.002$). However, this difference was not statistically significant when all studies of denosumab were pooled in the manufacturer's meta-analysis. Further safety data were available from 30 studies, giving a total of 14,000 patients, 11,000 of whom were postmenopausal women. These data came from clinical trials of other indications for denosumab, such as for preventing bone loss in breast cancer and prostate cancer. A review of this data by the US Food and Drug Administration concluded that patients receiving denosumab had a slightly higher incidence of serious infections of the skin, ear, urinary tract and abdomen, and more non-serious skin infections. The Food and Drug Administration considered denosumab to be safe, but had a concern about bone structure since biopsies showed suppression of dynamic bone formation parameters, which raised theoretical risks of delayed fracture healing and of atypical fracture. However, no statistically significant differences were observed for delayed fracture healing in the FREEDOM study (with two cases in patients receiving denosumab and four in patients receiving placebo).

The manufacturer's submission also examined adherence, persistence and compliance with treatment for osteoporosis. The following definitions were used:

- Adherence: 'a general term encompassing… persistence and compliance'.
- Persistence: '…the duration of time from initiation to discontinuation of therapy'.
- Compliance: '… the act of conforming to the recommendations made by the provider with respect to timing, dosage and frequency of medication taking… Compliance can be measured by the number of doses taken divided by the number of prescribed doses during a defined time period, also known as medication possession ratio (MPR)'. MPR is defined as 'the

sum of the days' supply of medication divided by the number of days between the first prescription and the end of the duration of the last prescription'.

Manufacturer's meta-analysis

Because only one study of denosumab measured fractures as an efficacy endpoint (FREEDOM), a meta-analysis was not necessary. An indirect comparison estimating the efficacy of denosumab with respect to all of the comparators was done.

A meta-analysis of studies comparing denosumab directly with alendronate using BMD endpoints was done to provide supporting evidence. This analysis was not used in the manufacturer's economic evaluation but was included in the appendices to the manufacturer's submission.

Manufacturer's indirect comparison

In the absence of head-to-head clinical trials of denosumab against all relevant comparators, the manufacturer estimated the effectiveness of denosumab relative to other osteoporosis treatments from an indirect comparison. This comparison included clinical trials of strontium ranelate, raloxifene, teriparatide, zoledronate and intravenous ibandronate compared with placebo. Studies used to inform the indirect analyses were identified from the manufacturer's systematic review, and a meta-analysis of the relative risks for each comparator against placebo was carried out. The manufacturer then estimated the adjusted indirect comparisons using the 'adjusted indirect comparison' method of Bucher et al. (1997) adopted for relative risk as the measure of treatment effect. The indirect estimate of denosumab against the comparator was adjusted according to the results of the direct comparison with placebo using both fixed and random effects meta-analyses.

The adjusted indirect comparison produced relative risks of fracture for denosumab compared to other drugs. [redacted] significantly

more effective than strontium ranelate (strontium) and raloxifene, [redacted] in preventing morphometric vertebral fracture (that is, a change in the form [size and shape] of the fracture). Denosumab was significantly more effective than strontium in preventing clinically diagnosed vertebral fracture. The relative risk for hip fracture was lower with denosumab than strontium ranelate (0.68) although it was not statistically significant. [redacted].

The results of the manufacturer's direct comparison of each comparator with placebo and the indirect comparison of denosumab with each comparator are summarised in Table 3 and 4.

Table 3 Manufacturer's direct comparison of each comparator with placebo from the random effects meta-analysis

Comparator	Clinically diagnosed vertebral fracture (relative risk [95% CI])	Non-vertebral fractures (relative risk [95% CI])	Hip fracture (relative risk [95% CI])	Wrist fracture (relative risk [95% CI])
Denosumab	0.32 (0.21 to 0.48)*	0.81 (0.69 to 0.96)*	0.61 (0.37 to 1.0)*	0.84 (0.64 to 1.1)
Zoledronate	0.23 (0.14 to 0.37)*	0.75 (0.65 to 0.87)*	0.59 (0.42 to 0.83)*	–
Raloxifene	0.45 (0.05 to 3.82)	0.66 (0.16 to 2.65)	–	–
Strontium ranelate	0.65 (0.50 to 0.84)*	0.88 (0.78 to 0.99)*	0.89 (0.67 to 1.2)	0.98 (0.73 to 1.31)

*Statistically significant ($p \leq 0.05$).

Table 4. Manufacturer's indirect comparison of denosumab with each comparator

Comparison	Morphometric vertebral fracture (relative risk [95% CI])	Clinically diagnosed vertebral fracture (relative risk [95% CI])	Non-vertebral fracture (relative risk [95% CI])	Hip fracture (relative risk [95% CI])	Wrist fracture (relative risk [95% CI])
Denosumab versus strontium ranelate	0.451 (0.324 to 0.627)*	0.488 (0.299 to 0.796)*	0.927 (0.755 to 1.138)	0.680 (0.388 to 1.192)	0.860 (0.575 to 1.286)
Denosumab versus raloxifene	0.501 (0.370 to 0.678)*	0.700 (0.079 to 6.165)	1.235 (0.304 to 5.029)		
Denosumab versus teriparatide					
Denosumab versus zoledronate					

*Statistically significant ($p \leq 0.05$).

The manufacturer also carried out a mixed treatment comparison to combine evidence from both direct and indirect comparisons in a single analysis using a Bayesian framework. The results of the manufacturer's mixed treatment comparison are in tables B24 and B25 on page 116 of the manufacturer's submission.

2.2 Evidence Review Group comments

The Evidence Review Group considered that the evidence of clinical effectiveness presented in the manufacturer's submission was derived from a large high-quality trial of adequate duration.

The group stated that they did not consider the evidence presented in the manufacturers submission on effects of drugs on BMD to be relevant because

of doubts about the value of BMD in assessing the effects of most drugs in osteoporosis, but mainly because fracture data were available for all the drugs. The group also noted that the data for morphometric vertebral fractures were not relevant, and such data were not used in the modelling.

The group expressed concerns about the relevant comparator for denosumab, the adjusted indirect comparison method used, and the methodology of the meta-regression to determine whether mean age and BMD were associated with different effects amongst treatments. The manufacturer's submission did not consider zoledronate and intravenous ibandronate to be the primary comparators for denosumab because they were used only in 0.7% and 0.6% of currently treated women (according to Intercontinental Marketing Services data), and neither comparator had been appraised by NICE. The Evidence Review Group stated that both ibandronate and zoledronate are licensed and used routinely in UK clinical practice for treatment of osteoporosis in postmenopausal women, and, in their view, zoledronate was the key comparator.

The manufacturer's submission included an indirect comparison in the absence of head-to-head clinical trials of denosumab against the relevant comparators. The Evidence Review Group noted several issues associated with the manufacturer's use of the 'adjusted indirect comparison' method of Buchner et al (1997). These include: the assumption that the size of the treatment effect is constant despite difference in baseline characteristics, estimation of a greater effect size than in a direct comparison, variation in the quality of studies with poorer studies over-estimating effect size, frequency of outcome dependent upon length of follow-up, and the variation in efficacy of treatment in different subgroups). The group noted that although the methodology used in the indirect comparison seemed sound and a thorough analysis of heterogeneity assumptions was done in the preceding meta-analysis, there are additional similarity assumptions for the indirect comparison. Furthermore the approach used to consider the effects of

differences in the baseline characteristics of the studies was not transparent, therefore, differences in baseline characteristics of the women in the trials (such as duration of follow-up, age, body-mass index, and proportion with previous fracture) would affect outcome comparisons. Furthermore the group noted that the similarity of the FREEDOM study to other studies was not adequately assessed with respect to factors that might modify the relative treatment effect (such as patients' characteristics, setting, and methodological quality). For further details please refer to pages 27 and 28 of the Evidence Review Group's report.

The Evidence Review Group noted that adherence is an important issue in osteoporosis treatment and identified review papers on adherence with oral bisphosphonates. The group noted that these reviews agreed with the manufacturer's statement that adherence with oral bisphosphonates is sub-optimal and therefore results in an increased fracture risk. Overall the group stated that adherence was given appropriate attention in the manufacturer's submission drawing on data from the General Practice Research Database.

2.3 Statements from professional/patient groups and nominated experts

The professional groups stated that the FREEDOM study was the primary randomised trial examining the effectiveness of denosumab versus placebo, in women aged 60–90 years with severe osteoporosis.

The professional groups noted that, overall, clinical trials have not reported increased adverse events for denosumab compared with current treatments. However, a meta-analysis of trial data showed an increased risk of infection and serious infections in patients receiving denosumab, which was of some concern. Therefore the professional groups suggested that screening may be necessary to exclude the presence of infection, and careful consideration should be given to use of denosumab in immunocompromised people.

In relation to current treatments used in UK clinical practice, the professional groups expressed the view that denosumab is as effective as oral bisphosphonates, with a greater degree of concordance and persistence with treatment because of the mode of administration. The professional groups expressed the view that denosumab has the same risk reduction as intravenous zoledronate for vertebral fracture, but that denosumab appears to have a greater risk reduction than oral bisphosphonates for vertebral fracture.

The patient's groups highlighted that reduction in the risk of fracture would have a substantial impact on the quality of life of patients, by increasing their confidence in performing activities of daily living, and exercise, and by improving general wellbeing. Professional and patient's groups noted that the effects of bisphosphonates persist beyond the treatment period because the bisphosphonate remains in the bones. The effects of denosumab are reversible on stopping treatment, which may be of benefit to patients who have concerns about the persistence of bisphosphonates.

Professional groups noted evidence that denosumab may have an advantage in people with osteoporosis and inflammatory disease such as rheumatoid arthritis, and in those receiving glucocorticoid treatment. Professional groups also noted uncertainty about denosumab's effect in subgroups with cancer (particularly breast cancer).

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's submission included a systematic review of the cost effectiveness evidence for denosumab, and the manufacturer carried out Markov cohort modelling to assess the cost effectiveness of denosumab against a range of comparators (split into primary and secondary comparators). Primary comparators included strontium ranelate, raloxifene and no treatment (placebo). Secondary comparators were intravenous

ibandronate, zoledronate and teriparatide. The manufacturer had stated that denosumab is expected to be a treatment option for people with osteoporosis in whom oral bisphosphonates are unsuitable (reasons for unsuitability include inability to comply with special instructions for administration, a contraindication or intolerance) and, therefore, comparisons with oral bisphosphonates were included in the appendices to the manufacturer's submission.

The model assessed the cost effectiveness of denosumab against the primary and secondary comparators for two separate cohorts. The first was the primary prevention of fragility fractures in women (70 years and over) with osteoporosis (T-score ≤−2.5) who cannot comply with or tolerate oral bisphosphonates. The second was the secondary prevention of subsequent fragility fractures in women (70 years and over) with osteoporosis (T-score ≤−2.5) and prior fragility fractures who cannot comply with or tolerate oral bisphosphonates. The model had a cycle length of 6 months and a lifetime horizon (defined as until time of death or age of 100 years) including a half-cycle correction.

The model included six discrete health states: well, hip fracture, clinically diagnosed vertebral fracture, wrist fracture, other types of fracture (pelvic, femur shaft, tibia, fibular, humerus, scapula, clavicle, rib and sternum), and death. It included two additional health states (post-hip fracture and post-vertebral fracture) to account for the long-term costs and effects associated with these fractures (no long-term costs or effects were assumed for patients with wrist or other fractures). When a fracture occurred, patients were modelled to remain in the respective fracture state for two cycles (1 year). After this period, patients with wrist fractures or other types of fracture were modelled to return to the well state. Those with vertebral fracture or hip fractures were modelled to enter a post-fracture state. Patients in the post-vertebral fracture state could then no longer incur a wrist fracture or other type of osteoporotic fracture (other than a subsequent vertebral fracture or hip

fracture). Those in the post-hip fracture state could only incur further hip fractures.

The manufacturer's base-case analysis assumed that patients continued osteoporosis therapy for 5 years and costs and quality adjusted life years were tracked over the lifetime of the cohorts (consistent with previous NICE guidance), and this assumption was examined in sensitivity analysis.

Subgroup analysis was undertaken for women with and without prior fracture by age and T-score. The T-score distribution (below the threshold) was divided into brackets of 0.1 standard deviations, and the relative risk attributable to each T-score bracket was estimated. The average risk below different T-score thresholds was estimated by taking the weighted average risk across all T-score brackets below the threshold (based on the proportions of the cohort in each bracket). Sensitivity analysis was conducted to assess cost effectiveness by the presence or absence of additional independent clinical risk factors for fracture in women 70 years of age, with and without prior fragility fractures.

Clinical evidence used in the modelling

In the manufacturer's base-case analysis, fracture risks were estimated on the basis of epidemiological literature. Fracture risks were based on three main elements:

- general population fracture risk
- increased fracture risk associated with osteoporosis
- risk reduction, if any, attributed to treatment.

A systematic review of the literature was undertaken to identify appropriate UK studies or systematic reviews for all three model parameters. Age-specific fracture risks were estimated for women in the general population (using a study by Singer et al. [1998] to estimate wrist and hip fractures, and a study by Kanis et al. [2000] to derive estimates for the incidence of clinically

diagnosed vertebral and other fractures). Next, age-matched Z-scores (that is, the estimate of the number of standard deviations below the general population's mean BMD for patient's age and sex) were estimated for a cohort with osteoporosis using the National Health and Nutrition Examination Survey (NHANES) III database. Evidence from the systematic review was then used to attribute age-specific relative risks for the different types of fracture. Treatment was modelled to continue for 5 years by applying relative risks to the estimated baseline risks of fracture in the cohort with osteoporosis. Following the termination of treatment after 5 years, an assumption was made that patients would return linearly to baseline risk levels over 1 year. (A return to baseline levels over the course of 5 years was assumed in previous NICE guidance). The relative risks of fracture for each treatment for clinical vertebral, hip and wrist fracture were estimated from the manufacturer's direct comparison for each treatment against placebo if data were available. If evidence was not available for a comparator, explicit assumptions were employed:

- the relative risk for clinical vertebral fracture was assumed to be equivalent to morphometric relative risk data for interventions that lacked clinical vertebral fracture data
- the relative risk for interventions with missing wrist and hip fracture was assumed to be 1.00
- since no efficacy evidence was identified for intravenous ibandronate compared with placebo, efficacy was assumed to be equivalent to oral ibandronate
- the relative risk for other fracture was assumed to be equivalent to 1.00 for all therapies because 'other fracture' was not consistently defined across studies.

Please refer to Table 3 for the estimates of relative risk used in the manufacturer's submission.

The model accounted for observed increases in the risk of mortality after fracture, by applying relative risks for mortality obtained from a review of the literature. An increased risk was modelled for the first and subsequent years post-hip fracture and post-vertebral fracture. For other types of fracture, patients were modelled to be at increased risk of mortality for 1 year only. The relative risks for mortality after all types of fracture were adjusted downwards to account for the observation that a substantial proportion of mortality after fracture can be explained by comorbidity. An assumption was made that 30% of all mortality after all types of fracture is causally related, which is consistent with similar assumptions in TA160 and TA161.

An alternative risk estimation algorithm, FRAX, was applied in a sensitivity analysis to estimate fracture risk in cohorts of women at defined T-scores with and without additional independent clinical risk factors for fracture.

The manufacturer's model also took into account adherence, persistence and compliance. An adherence modelling framework proposed by Strom et al. (2006) was used in the manufacturer's model. Persistence and compliance were assumed to be 100% for the 5-year treatment period for all modelled treatments. Sensitivity analysis was carried out for persistence and compliance (the latter was for oral therapies only).

Table 5 provides a summary of parameters and assumptions applied in the manufacturer's base-case analyses.

Table 5. Summary of manufacturer's parameters and assumptions applied in the base-case analysis (reference from manufacturer's submission)

Variable	Value	Distribution (model range)	Reference
Age at treatment start (years)	70	Deterministic (55–75)	Section 6.2
T-score (SD)	≤ −2.50	Deterministic (−1.0 to −4.0)	Section 6.2
Proportion with previous vertebral fracture	0 or 1	Deterministic (0–1)	Section 6.2
Discount rates for costs and effects	3.50%	Deterministic (0–6%)	Section 6.2
Treatment duration (years)	5	Deterministic (5 years – lifetime)	Section 6.2
Modelling horizon	Lifetime	Deterministic (10 years – lifetime)	Section 6.2
Gastrointestinal adverse event modelling (oral therapies)	2.35%	Deterministic	Section 6.4
Cellulitis modelling (denosumab)	0.3%	Deterministic	Section 6.4
Adjustment for missed fractures	No	Deterministic	Section 6.2
Persistence	No	Deterministic	Section 6.2
Compliance	No	Deterministic	Section 6.2
Number of DXA scans per year (all treatments)	0.5	Deterministic	Section 6.2
Maximum offset time (years)	1	Deterministic	Section 6.2
Utility			
Population utility	Age dependent	Deterministic	Section 6.4
Utility multiplier fracture	Fracture dependent	Beta	Section 6.4
Utility multiplier – gastrointestinal adverse events	0.91	Beta	Section 6.4
Utility multiplier – cellulitis	0.82	Beta	Section 6.4
Costs			
Drug therapy costs	Therapy dependent	Deterministic	Section 6.5
BMD monitoring	£33	Gamma	Section 6.5
GP visit	£37	Deterministic	Section 6.5
Gastrointestinal adverse events – course H_2-antagonists	£2.37	Deterministic	Section 6.5
Cellulitis hospital admission	£1,437	Lognormal	Section 6.5
Fracture Healthcare Resource Group costs	Age dependent	Lognormal	Section 6.5
Nursing home costs per year	£25,269	Deterministic	Section 6.5
Fracture risk			
General population	Age dependent	Deterministic	Section 6.3
Relative risk fracture by	Age and fracture	Deterministic	Section 6.3

Variable	Value	Distribution (model range)	Reference
BMD	dependent		
Relative risk fracture by prior fracture status	Age and fracture dependent	Deterministic	Section 6.3
Relative risk of fracture, all comparators versus placebo	Meta-analysis	Lognormal	Section 5.7 [a] and 6.3.1[a]
Mortality post fracture	Age and fracture dependent	Deterministic	Section 6.3
Patients entering nursing home post-hip fracture	Age dependent	Deterministic	Section 6.3
Proportion of patients day case/admitted/surgery	Age independent	Dirichelet	Section 6.3

DXA = dual energy X-ray absorptiometry. BMD = bone mineral density. GP = general practitioner

[a] Data sourced from meta-analyses – see Table 3(section 5.7.6 of manufacturer's submission) Probabilistic Sebnsitivity Analysis uses 95% confidence intervals around the hazard ratio.

Utility and costs

The EQ-5D questionnaire was administered to patients in the FREEDOM study, but the number of fracture events with associated EQ-5D scores recorded was low and the trial design precluded assessment of health status immediately after fracture events. Thus, evidence from the manufacturer's systematic review of the health-related quality of life literature in osteoporosis was considered to be more meaningful and was applied in the economic analysis. Utility decrements associated with fracture were obtained from a systematic review of the literature and applied to population norms in the form of utility multipliers. Utility loss associated with hip and vertebral fracture was modelled in a two-stage process, with a larger decrement in the first year after fracture and an ongoing but less severe utility penalty in subsequent year. Utility multipliers for the first and subsequent years following hip fracture were obtained from a meta-analysis of studies utilising the EQ-5D responses. Utility loss associated with clinically diagnosed vertebral fracture was estimated separately for the proportions of patients managed in hospital and in primary care. Patients in hospital were assumed to incur decrements derived from the EQ-5D scores of a cohort that were predominantly in hospital. People who were not in hospital were assumed to incur decrements obtained from cohorts

with prevalent morphometric fractures. Utility multipliers associated with wrist fracture were also obtained from the literature and applied in the model for 1 year after the event. Because of an absence of evidence, the same multiplier and the same approach were also used to model utility loss associated with other types of fracture. Finally, utility decrements associated with selected adverse events were also included in the model. The utility values used in the manufacturer's model are summarised in Table 6.

Table 6 Summary of utility values used in the manufacturer's submission

State	Utility multiplier	Confidence interval	Justification
Well 50 years	0.82*	–	General population EQ-5D tariff values for the UK. Systematic review of the literature indicated no utility loss for osteoporosis without fracture.
Well 60 years	0.78*	–	
70 years	0.72*	–	
80 years +	0.69*	–	
Hip fracture year 1	0.70	0.64 to 0.77	The systematic review of the literature concluded that pooled EQ-5D data reported in Peasgood et al. (2009) were appropriate to estimate health-related quality of life for patients with hip fracture at year 1 and years 2+.
Hip fracture years 2–5	0.80	0.68 to 0.96	
Vertebral fracture year 1 (in hospital)	0.64	0.57 to 0.73**	Estimates taken from Borgstrom et al. (2006), and Ström et al. (2008b) were identified as the most appropriate source of data for clinically diagnosed vertebral patients in hospital by the systematic review. Oleksik et al. (2000) was the most appropriate data source for patients not in hospital. Estimates from Cockerill et al. (2004) applied for years 2+ for patients not in hospital.
Vertebral fracture year 1 (non-hospital)	0.91	–	
Vertebral fracture years 2–5 (in hospital)	0.73	0.62 to 0.82**	
Vertebral fracture years 2–5 (non-hospital)	0.99	–	
Wrist fracture	0.934	0.911 to 0.956**	Estimates taken from pooled analysis Ström et al. (2008) EQ-5D data for wrist fracture patients assuming 4-month utility reached after 1 month.
Other fracture	0.934	0.911 to 0.956**	Utility values for other fractures poorly or not reported. Wrist fracture utility values applied as a conservative estimate.
Dead	0	–	Utility assumed to be measured on a 0–1 scale in which 0 = death
Gastrointestinal adverse events	0.91	0.87 to 0.96	Groeneveld (2001) Previously employed in NICE Health Technology Assessment reviews. Applied for consistency
Cellulitis	0.82	0.79 to 0.85	Redekop et al. (2004) – assumption that utility multiplier equivalent to patients with leg ulcers

*Mean utility. **Calculated from Strom et al. (2008) using confidence interval for utility loss.

Treatment costs and quality of life decrements associated with wrist or other types of fracture were modelled to last 1 year, and clinically diagnosed vertebral fractures and hip fractures were modelled to incur ongoing costs and loss of quality of life.

Resource use in the model consisted of: drug treatment was estimated using the British National Formulary with assumptions for costs of administration monitoring for the comparators. Fracture costs were estimated using hospital episode statistics for England and Wales in conjunction with the Department of Health Healthcare Resource Group tariff, assumptions surrounding the proportion of patients treated in hospital, with and without, surgery, for the different fracture types were informed by a combination of expert opinion, review of literature and analysis of routine data. Costs associated with severe adverse events were included (such as gastrointestinal adverse events associated with oral therapies and cellulitis associated with denosumab). Other types of adverse events associated with denosumab and its comparators were excluded.

Unit costs associated with the primary and secondary comparators used in the manufacturer's submission are presented in Table 7, and costs associated with each of the health states in the manufacturer's economic model are outlined in Table 8.

Table 7 Unit costs associated with the primary and secondary comparators in the manufacturer's economic model

Resource use per annum	No treatment	Denosumab	Strontium ranelate	Zoledronate	Ibandronate	Raloxifene	Teriparatide
Brand (purchase dose)	–	Prolia (60 mg)	Protelos (2 g – 28 sachets)	Aclasta (5 mg)	Bonviva (3 mg syringe)	Evista (60 mg 28 tablets)	Forsteo (3 ml pen 28 doses)
Technology cost	–		£25.60	£283.74	£68.64	£17.06	£271.88
Dosing	–	60 mg/ biannually	2 g/day	5 mg/year	3 mg/every 3 months	60 mg/day	£0.00
Mean cost per year	£0.00	£366.00	£333.71	£283.74	£274.56	£222.39	£3,544.15
Administration: doses per year	–	2	365	1	4	365	365
Route of administration	–	Subcutaneous injection	Oral	Intravenous	Intravenous	Oral	Subcutaneous injection
Administration cost*	–	£37.23	–	£163.80	£657.66	–	£37.23
Monitoring cost (1 general practice visit per year)	£0.00	£37.23	£37.23	£37.23	£37.23	£37.23	£37.23
BMD monitoring (once every 2 years)	£0.00	£33.18	£33.18	£33.18	£33.18	£33.18	£33.18
Total cost per year	£0.00	£473.65	£404.13	£517.95	£1,002.63	£292.80	£3,651.80

*Additional monitoring or administration management in general practice assumed for subcutaneous injections
BMD = bone mineral density

Table 8 Costs associated with health states in the manufacturer's economic model

Health states	Items	Proportion of patients	Indexed costs 2009 (women 60–74 years)	Indexed costs 2009 (women 75+ years)
All health states	Drug therapy costs	All	Therapy dependent	Therapy dependent
	BMD monitoring costs every 2 years	All	£33	£33
	General practice visit		£37	£37
	H_2 antagonists	Therapy dependent	£2.20	£2.20
Well	–	–	–	–
Hip fracture	Hip fracture cost	All	£9,165	£10,560
	Nursing home costs	All	£25,201	£25,201
Vertebral fracture	Vertebral fracture cost	All	£1,318	£1,581
Wrist fracture	Wrist fracture cost	All	£2,311	£2,771
Other fracture	Other fracture cost	All	£2,510	£3,747
Hip fracture post-vertebral fracture	Hip fracture cost	All	£9,165	£10,560
	Nursing home costs per year	All	£25,201	£25,201
Vertebral fracture post-hip fracture	Vertebral fracture cost	All	£1,318	£1,581

Results

The results for the manufacturer's base-case analyses for both primary and secondary comparators are presented in Tables 9 and 10.

Table 9 Primary comparisons: manufacturer's base-case cost effectiveness for denosumab, strontium ranelate, raloxifene and no treatment

				Versus lowest cost comparator			ICER versus low-cost comparator		ICER for comparison with denosumab[a]	
	LY	QALY	Cost (£)	Δ LY	Δ QALY	Δ Cost	LY	QALY	LY	QALYs
No prior fracture										
No treatment	11.606	7.991	9,455	0.000	0.000	0	–	–	47,220	29,223
Raloxifene[b]	11.628	8.009	10,764	0.022	0.018	1,310	60,786	74,239	26,383	9,289
Denosumab	11.642	8.048	11,135	0.036	0.057	1,680	47,220	29,223	–	–
Strontium ranelate	11.622	8.007	11,138	0.016	0.016	1,684	104,069	102,592	Denosumab dominant	Denosumab dominant
Prior fracture										
No treatment	11.492	7.797	12,060	0.000	0.000	0	–	–	17,719	12,381
Raloxifene	11.548	7.852	13,410	0.056	0.055	1,351	24,021	24,524	4,820	2,046
Denosumab	11.576	7.917	13,543	0.084	0.120	1,483	17,719	12,381	–	–
Strontium ranelate	11.531	7.841	13,698	0.039	0.044	1,638	41,767	37,123	Denosumab dominant	Denosumab dominant

ICER = incremental cost effectiveness ratio. LY = life years. QALY = quality adjusted life year. Δ =change

[a] Pairwise ICERs for denosumab versus each strategy are presented to demonstrate the cost-effectiveness of denosumab relative to the existing guidance recommendations in TA160 and TA161.

[b] Raloxifene is not recommended by NICE for patients with no prior fracture.

Table 10 Secondary comparisons: manufacturer's base case cost effectiveness result for denosumab, intravenous ibandronate, zoledronate and teriparatide

				Versus lowest cost comparator			ICER versus low-cost comparator	
	LY	**QALY**	**Cost (£)**	**Δ LY**	**Δ QALY**	**Δ Cost**	**LYs**	**QALYs**
No prior fracture								
Denosumab	11.642	8.048	11,135	0.000	0.000	0	–	–
Zoledronate	11.646	8.053	11,490	0.004	0.005	355	88,386	70,900
Ibandronate (intravenous)	11.624	8.011	13,890	−0.017	−0.037	2,756	Denosumab dominant	Denosumab dominant
Teriparatide*	11.648	8.066	24,710	0.007	0.018	13,576	2,073,082	772,424
Prior fracture								
Denosumab	11.576	7.917	13,543	0.000	0.000	0	–	–
Zoledronate	11.586	7.930	13,903	0.010	0.012	360	34,292	29,029
Ibandronate (intravenous)	11.540	7.849	16,526	−0.036	−0.068	2,984	Denosumab dominant	Denosumab dominant
Teriparatide	11.584	7.947	26,867	0.008	0.030	13,324	1,580,601	451,269

ICER = incremental cost effectiveness ratio. LY = life years. QALY = quality adjusted life year. Δ =change
ICERs compared with denosumab are not presented separately, because denosumab is the lowest cost treatment in this scenario
*Teriparatide is not recommended by NICE in patients with no prior fracture. NICE have not appraised ibandronate iv or zoledronate iv.

The manufacturer presented a subgroup analysis to demonstrate how cost effectiveness varied using different treatment cut-offs (that is, all women with a T-score 'at or below' −2.5, −3,−3.5, et cetera). The manufacturer provided further subgroup analyses at the request of the Evidence Review Group for women with and without prior fracture by age and T-score. The manufacturer also provided a subgroup analysis using the FRAX algorithm showing how cost effectiveness varied by T-score and the presence or absence of independent clinical risk factors for fracture. For results of the manufacturer's subgroup analyses please refer to tables 11–14 on pages 59–62 of the

Evidence Review Group's report, and to tables 15–18 on pages 63–70 of the report for the results of the subgroup analyses using the FRAX algorithm. The results presented in tables 11 and 12 show that cost effectiveness improves as age increases and T-score decreases, and with the presence of prior fragility fracture. Analysis using the FRAX algorithm demonstrates that the presence of independent clinical risk factors, particularly rheumatoid arthritis also improves the cost effectiveness of denosumab compared with the primary comparators.

The manufacturer conducted a range of deterministic and probabilistic sensitivity analyses. The results of the deterministic analyses showed that alterations to most key parameters had limited impact on comparisons between denosumab and raloxifene, strontium ranelate, and no treatment. The impact on comparisons with intravenous ibandronate, zoledronate and teriparatide were most sensitive to changes in cost assumptions for administration of denosumab. Following a request from the Evidence Review Group, the manufacturer provided an analysis in which the cost of administering denosumab was increased to assess cost effectiveness if it were delivered in secondary care. Under this scenario, the incremental cost effectiveness ratio (ICER) for denosumab rose to £36,185 per QALY gained in those with no prior fragility fracture, and £15,720 in those with a prior fragility fracture. This change led to zoledronate dominating denosumab in women with and without a prior fragility fracture. After a further request from the Evidence Review Group, the manufacturer carried out sensitivity analysis in which denosumab was assumed to be initiated in secondary care and thereafter delivered in general practice.

The manufacturer provided further analysis at the request of the Evidence Review Group, to assess equal efficacy of denosumab and zoledronate for the prevention of wrist fractures. This analysis showed that the ICER for denosumab appeared to be moderately sensitive to assumptions regarding

the relative efficacy of the two drugs for the prevention of wrist fractures (see page 24 of the manufacturer's response to clarification 4th March 2010).

The results of the manufacturer's probabilistic sensitivity analysis showed that denosumab had approximately a 50% probability of being considered cost effective at a payment threshold of £30,000 per QALY gained compared with the primary comparators (in the base case population of women aged 70 years with a T-score at or below −2.5 and no prior fracture), increasing to 90% in women with a prior fragility fracture. Against the secondary comparators, denosumab had a 0.7% and 0.6% probability of being considered cost effective at a payment threshold of £30,000 per QALY gained (in the base-case population of women aged 70 years with and without prior fractures respectively).

3.2 Evidence Review Group comments

The Evidence Review Group noted that the manufacturer provided multiple comparisons of cost effectiveness using a high quality validated model which took into account a wide range of costs such as short-term drug costs and long-term nursing home costs, and the analysis met the NICE reference case. The group considered that the appendices also provided very detailed accounts of underlying model assumptions and sensitivity analyses.

Several problems with the manufacturer's economic model were identified by the Evidence Review Group, specifically:

- choice of comparator
- cost assumptions for denosumab
- validity of assumptions used for modelling utilities, costs, persistence and compliance
- varied cost effectiveness in subgroups of the cohort modelled
- omission of underlying fracture risk estimates from the probabilistic sensitivity analysis
- treatment setting and administration of denosumab.

First, the Evidence Review Group believed that zoledronate was the key comparator. The second issue was that the group viewed that the relative cost-effectiveness of denosumab compared with zoledronate depended upon assumptions made about relative costs. In the manufacturer's submission a key assumption was that denosumab would be given twice a year in general practice at the average cost of two standard visits to a GP, whereas zoledronate was assumed to be given once a year in hospital clinics (with some monitoring incorporated into the visit). The Evidence Review Group believed that this approach had the effect of making denosumab much less costly than zoledronate. Therefore the group believed that given the similar effectiveness of denosumab and zoledronate, the cost effectiveness comparison depended largely on the relative costs used in the model.

The Evidence Review Group identified that a simplifying assumption was used regarding the transitions in the model, in which individuals experiencing a vertebral fracture could no longer experience a wrist fracture or other type of fracture (apart from clinical vertebral fractures or hip fractures). After a hip fracture individuals could no longer experience any type of fracture other than a subsequent hip fracture. The Evidence Review Group believed that this assumption was unrealistic because experience of a hip or clinical vertebral fracture would put individuals at higher risk of further fracture, however the effect on the cost effectiveness estimates was unclear.

The Evidence Review Group noted that in the manufacturer's base-case analysis, the assumption that fracture risk would return linearly to baseline levels over the course of 1 year after discontinuation of treatment was a conservative assumption that would favour oral therapies. Persistence and compliance were assumed to be 100% for all treatments in the base-case analysis, which was also a conservative assumption. The Evidence Review Group noted that after initial administration of denosumab, both compliance and persistence will be 100% for 6 months. However, in the long-term, persistence with denosumab therapy may be less than 100%. The

manufacturer carried out sensitivity analyses which examined variations in persistence for oral therapies, but variation of persistence with denosumab was not examined.

The Evidence Review Group noted that the manufacturer's quality of life review methodology and the primary studies included in the review suggested that suitable utility multipliers had been applied in the model. However, many of the multipliers were derived from observational time-series studies without independent control groups and therefore did not control for all potential confounding factors. The group noted that costs and utility losses associated with wrist fractures and other types of fracture were assumed to last for 1 year, whereas hip fractures and clinical vertebral fractures were modelled to incur ongoing costs and utility losses. They also noted that utility loss relative to population norms remained at a constant rate in the second and subsequent years post-hip fracture and post-vertebral fracture, therefore this assumption may slightly overestimate utility loss associated with hip and vertebral fracture if the observed trend towards improved quality of life in the second year post-fracture were to continue in subsequent years.

The Evidence Review Group noted that the manufacturer's ICERs vary substantially within subgroups within the cohorts, and that the appropriate comparator also varies by subgroup according to existing NICE guidance. Furthermore, neither raloxifene or strontium ranelate compare favourably with no treatment (ICERs £74,239 and £102,529 per QALY gained respectively for 70 year old women with no prior fragility fracture and a T-score of −2.5 SD, and £24,524 and £37,123 per QALY gained respectively for women with a prior fragility fracture), which is consistent with the modelling carried out for TA160 and TA161.The Evidence Review Group expressed the view that demonstrating cost effectiveness against these comparators does not allow the conclusion that denosumab is cost effective. The group also believed that for the comparison between denosumab and zoledronate there was uncertainty relating to costs of administering these two drugs and their relative

efficacy for the prevention of wrist fracture. Based on the manufacturer's base-case analysis, the comparison of denosumab with oral bisphosphonates suggests that denosumab may be a be a cost effective option for patients who cannot take alendronate (ICER £21,189 per QALY gained compared with risedronate and £8680 compared with oral ibandronate in the lower risk cohort, that is 70 year old women with no prior fragility fracture and a T-score of −2.5). Therefore, for those who cannot take oral alendronate, denosumab might be considered cost-effective compared with risedronate and or oral ibandronate.

The manufacturer conducted a range of deterministic and probabilistic sensitivity analyses. The Evidence Review Group noted that an important omission from the probabilistic sensitivity analysis was the underlying estimates of fracture risk. The manufacturer stated that data limitation meant that distributions could not be estimated for these parameters. The group believed that this would have the effect of overestimating the probability of denosumab being considered cost effective at different payment thresholds, and it was noted that deterministic sensitivity analysis showed that the cost effectiveness estimates were sensitive to underlying fracture risk.

The Evidence Review Group had concerns about the treatment setting and administration of denosumab. The subcutaneous injection of denosumab is simple and could be given by a general practitioner, practice nurse or the patient themselves. However, the Evidence Review Group believed that denosumab would probably not be started in general practice because it is a new biological agent with effects on other body systems (including the immune system) and the occurrence of long-term adverse events cannot be ruled out. The group stated that they would expect at least one outpatient visit to be needed and, in many cases, continued hospital follow-up would be necessary. Therefore, if follow-up was partly or mainly in general practice, the Evidence Review Group believed that it was unlikely that administration of denosumab would probably not be provided in primary care as part of general

medical services, and would be regarded as an enhanced service for which an additional payment would be negotiated (the size of which is currently unknown, but may be greater than the average cost of two visits to a GP per patient). Therefore, the marginal costs per patient of administering denosumab in primary care may be greater than the average cost of two general practice visits per year as presented in the manufacturer's model.

The Evidence Review Group noted that denosumab could be self-administered by the patient, but that the average age of women taking medication for the prevention of fracture in the General Practice Research Database dataset was 71.4 years, and many would be older than that. Such patients might not be able to give themselves the subcutaneous injection due to poor eyesight or manual dexterity, or cognition problems. The oldest age groups also have the highest proportion of patients treated with bisphosphonates, which the manufacturer expects denosumab to be an alternative to. Furthermore, training women to self-administer denosumab might not be regarded as worthwhile since they would have to visit a general practice to obtain the pre-filled pen injection device, and after 6 months some may have forgotten how to administer it, which is unlikely to occur with drugs given daily, for example teriparatide. The Evidence Review Group expressed the view that an equality issue existed for women who had experienced a stroke in the past and who are at increased risk of falls and fracture, together with bone loss due to reduced mobility. Such patients might have difficulty swallowing or standing to take oral bisphosphonates and therefore intravenous or subcutaneous drugs may be more suitable.

3.3 Further considerations following premeeting briefing teleconference

Equality and diversity

No equalities issues were raised during the scoping process or the evidence collection for this appraisal.

An overview of the equalities issues considered in TA160 for women who cannot take alendronate is as follows:

- The Committee noted that at least some women who cannot take alendronate (because of a condition that either makes alendronate contraindicated or which prevents individuals from complying with the instructions for administration) 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.
- 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. 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 preventive treatment for all patients with the same level of risk. The Committee noted that the ICERs for these drugs compared with no treatment were very high. 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. The Committee considered the fact that the impact of refusing the more favourable recommendation is that no preventive treatment is generally recommended for a particular group of patients who are at the lower end of fracture risk for which treatment was considered, but that alternative drugs are recommended when these patients are at higher risk of fracture.

- The Committee considered that maximising the number of patients who are able to take alendronate is important. Some women who have a disability leading to difficulty complying with the instructions for administration of alendronate could receive it if they received assistance in taking it. The Committee concluded that all reasonable steps should be taken to provide these women 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 Authors

Fay McCracken (Technical Lead) and Helen Knight (Technical Adviser), with input from the Lead Team (Jonathan Michaels, Usha Chakravarthy and Paddy Storrie).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group report for this appraisal was prepared by Aberdeen Health Technology Assessment Group:

- Scotland G et al. Evidence review: denosumab for the prevention of osteoporotic fractures in post-menopausal women (March 2010).

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Amgen

II Professional/specialist, patient's/carer's and other groups:

- Royal College of Nursing
- Royal College of Pathologists
- Society and College of Radiographers
- National Osteoporosis Society
- North Bristol NHS Trust / University of Bristol

Appendix B: Recommendations from published NICE technology appraisals

TA160 Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women

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

	Number of independent clinical risk factors for fracture (see section 1.5)		
Age (years)	**0**	**1**	**2**
65–69	–[a]	−3.5	−3.0
70–74	−3.5	−3.0	−2.5
75 or older	−3.0	−3.0	−2.5

[a] 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

	Number of independent clinical risk factors for fracture (section 1.5)		
Age (years)	**0**	**1**	**2**
65–69	– [a]	−4.5	−4.0
70–74	−4.5	−4.0	−3.5
75 or older	−4.0	−4.0	−3.0

[a] 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/m2), medical conditions such as ankylosing spondylitis, Crohn's disease,

conditions that result in prolonged immobility, and untreated premature menopause1.

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 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.

[1] Rheumatoid arthritis is also a medical condition indicative of low BMD.

TA161 Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

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

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

1.2 Risedronate and etidronate are recommended as alternative treatment options for the secondary 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 1.6) **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

	Number of independent clinical risk factors for fracture (section 1.5)		
Age (years)	**0**	**1**	**2**
50–54	– [a]	−3.0	−2.5
55–59	−3.0	−3.0	−2.5
60–64	−3.0	−3.0	−2.5
65–69	−3.0	−2.5	−2.5
70 or older	−2.5	−2.5	−2.5

[a] Treatment with risedronate or etidronate is not recommended

If a women aged 75 years or older 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 and raloxifene are recommended as alternative treatment options for the secondary 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 1.6) **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 or raloxifene is recommended when alendronate and either risedronate or etidronate cannot be taken

	Number of independent clinical risk factors for fracture (section 1.5)		
Age (years)	**0**	**1**	**2**
50–54	– [a]	−3.5	−3.5
55–59	−4.0	−3.5	−3.5
60–64	−4.0	−3.5	−3.5
65–69	−4.0	−3.5	−3.0
70–74	−3.0	−3.0	−2.5
75 or older	−3.0	−2.5	−2.5

[a] Treatment with raloxifene or strontium ranelate is not recommended

If a woman aged 75 years or older who has one 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.

For the purposes of this guidance, indicators of low BMD are low body mass index (defined as less than 22 kg/m^2), medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, and untreated premature menopause[2].

In deciding between strontium ranelate and raloxifene, clinicians and patients need to balance the overall proven effectiveness profile of these drugs against their tolerability and other effects in individual patients.

[2] Rheumatoid arthritis is also a medical condition indicative of low BMD.

1.4 Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to take 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 1.6), **or** who have a contraindication to, or are intolerant of strontium ranelate (as defined in section 1.7), **or** who have had an unsatisfactory response (as defined in section 1.8) to treatment with alendronate, risedronate or etidronate **and**
- who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, **or** who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures.

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, 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.

1.7 For the purposes of this guidance, intolerance of strontium ranelate is defined as persistent nausea or diarrhoea, either of which warrants discontinuation of treatment.

1.8 For the purposes of this guidance, an unsatisfactory response is defined as occurring when a woman has another fragility fracture

despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below her pre-treatment baseline.

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.

Appendix C: Appropriate comparators for denosumab

Appropriate comparators for denosumab by prior fracture status, age, T-score and clinical risk, based on current NICE guidance, for those unable to tolerate oral bisphosphonates (taken from page 39 of the Evidence Review Group's report)

	Number of independent clinical risk factors		
No prior fragility fracture	**0**	**1**	**2**
Age 65–69 years (T-scores)			
−2.5	No treatment	No treatment	No treatment
−3.0	No treatment	No treatment	No treatment
−3.5	No treatment	No treatment	No treatment
−4.0	No treatment	No treatment	Strontium ranelate
−4.5	No treatment	Strontium ranelate	Strontium ranelate
Age 70–74 years (T-scores)			
−2.5	No treatment	No treatment	No treatment
−3,0	No treatment	No treatment	No treatment
−3.5	No treatment	No treatment	Strontium ranelate
−4.0	No treatment	Strontium ranelate	Strontium ranelate
−4.5	Strontium ranelate	Strontium ranelate	Strontium ranelate
Age ≥75 years (T-scores)			
−2.5	No treatment	No treatment	No treatment
−3.0	No treatment	No treatment	Strontium ranelate
−3.5	No treatment	No treatment	Strontium ranelate
−4.0	Strontium ranelate	Strontium ranelate	Strontium ranelate
−4.5	Strontium ranelate	Strontium ranelate	Strontium ranelate
Prior fragility fracture			
Age 50–54 years (T-scores)			
−2.5	No treatment	No treatment	No treatment
−3.0	No treatment	No treatment	No treatment
−3.5	No treatment	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.0	No treatment	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.5	No treatment	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
Age 55–59 years (T-scores)			
−2.5	No treatment	No treatment	No treatment
−3.0	No treatment	No treatment	No treatment
−3.5	No treatment	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.0	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.5	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene

Age 60–64 years (T-scores)			
−2.5	No treatment	No treatment	No treatment
−3.0	No treatment	No treatment	No treatment
−3.5	No treatment	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.0	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.5	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
Age 65–69 years (T-scores)			
−2.5	No treatment	No treatment	No treatment
−3.0	No treatment	No treatment	Strontium ranelate /raloxifene
−3.5	No treatment	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.0	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.5	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
Age 70–74 years (T-scores)			
−2.5	No treatment	No treatment	Strontium ranelate /raloxifene
−3.0	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−3.5	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.0	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.5	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
Age ≥75 years (T-scores)			
−2.5	No treatment	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−3.0	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−3.5	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.0	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene
−4.5	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene	Strontium ranelate /raloxifene