NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Denosumab for the Prevention of Osteoporotic Fractures in Postmenopausal Women

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Amgen	All of the relevant evidence has been taken into account	Comment noted
Amgen	Amgen welcomes the Appraisal Committee's acknowledgement of the high quality of the clinical data submitted and of the economic evaluation. However, the Appraisal Committee noted some concern about the economic model and we have taken this opportunity to provide further reassurance with respect to the omission of underlying fracture risk estimates from the probabilistic sensitivity analysis and the long-term effects of fractures on mortality and nursing home care. • Omission of underlying fracture risk estimates from the probabilistic sensitivity analysis (Section 3.28 of the ACD, Section 5.28 of ERG report) Concern has been raised by the ERG that a probabilistic distribution has not been applied for baseline fracture rates and that this may bias the analyses in favour of denosumab. In order to address this concern, we have conducted a further sensitivity analysis, which showed little impact on the results. The rates employed in the base case are based on Singer et al (1998). For women aged 70-74 the sample size is given as 15,875, falling to 10,750 for age 80-84. It can be expected that with these sample sizes, confidence intervals around the mean estimates would be relatively narrow. We explored the effect of assigning beta distributions to baseline fracture incidence based on an assumed sample size of 10,000 for each parameter. A probabilistic run of the base case scenario of a patients aged 70 with T-score -2.5 and no prior fracture, produced an Incremental Cost-Effectiveness Ratio (ICER) for denosumab against no treatment of £30,422, little different from the deterministic result of £29,223. This is a crude analysis, with, for example, no account taken of the difference in precision of estimates at different ages. Moreover, in some cases the mean estimates are very low, and the beta-distribution (based on the binomial) does not perform well where the mean is close to zero. Data to support regression methods is not available, however, and, though other distributions may be more appropriate, any analysis will remain crude in the absence of more completely reported source data. This exploratory analysis demonstrates the addition of probabilistic distributions to baseline fracture risk may be minimal, even under the crude, exploratory approach we have adopted.	Comment noted. Please see FAD section 3.36.

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<td>Amgen</td>
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- Long-term effects of fractures on mortality and nursing home care (Sections 4.10 and 4.11 of the ACD)

Whilst the Appraisal Committee concluded in the ACD that the long term effects of fractures on mortality and nursing home care did not have a substantial impact on the cost effectiveness estimates for denosumab, we are keen to address the question raised on this point in the ACD. The model does not track the mortality of patients admitted to nursing home separately from that of other patients. In practice patients admitted to nursing homes following fracture may be at higher risk of mortality than those who are not admitted, in which case, as has been pointed out, the model may exaggerate the impact of nursing home admission on costs and utilities. The sources used to provide relative risks for mortality following fracture can be expected to capture, to the degree nursing home admission occurred in the study populations, the higher rate of mortality in these patients.
Nevertheless, in order to ensure no bias is introduced relating to the additional costs and utility impacts of nursing home admission, sensitivity analyses were run in which nursing home admission is set to zero. This is an extreme and unrealistically conservative assumption. As per the Appraisal Committee's conclusion, this does not have a substantial impact on the results.

Base case and sensitivity analyses on nursing home admission following fracture

No prior fracture	**Strontium**	**Raloxifene**
Base case	dominant	9,289
Zero nursing home admission	2,040	12,438

Prior fracture	**Strontium**	**Raloxifene**
base case	dominant	2,046
Zero nursing home admission	dominant	5,120

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<td>Sections 3.14 and 4.12 of the FAD state that the Committee noted the manufacturer's additional sensitivity analyses using the assumption that nursing home admission was zero. The Committee concluded that the long-term effects of fractures on mortality and nursing home care had only a minor impact on the cost-effectiveness estimates for denosumab.</td>
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Amgen	We would also like to take this opportunity to correct some factual mistakes noted in the ACD and to suggest alternative wording in instances where more precise language will leave no room for misinterpretation. The table below reviews these points according to the numbering used in the ACD. Section 2.2 states: The summary of product characteristics states that the following conditions may be associated with denosumab treatment: eczema, diverticulitis, cataracts, hypocalcaemia, and skin infections (predominantly cellulitis). This is correct, however it is important to point out that imbalances in the incidence of cataract and diverticulitis were not observed in PMO patients; their inclusion in this statement reflects observations in prostate cancer patients undergoing HALT. The summary of product characteristics (Section 4.5) states with regard to cataracts "No imbalance was observed in postmenopausal women with osteoporosis or in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer", and with regard to diverticulitis, "The incidence of diverticulitis was comparable between treatment groups in postmenopausal women with osteoporosis and in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer". Data for cataract were presented in Table B33 (p 132) of Amgen's restructured submission (dated 15 February 2010). Proposed text: The summary of product characteristics states that the following conditions may be associated with denosumab treatment: eczema, diverticulitis, cataracts, hypocalcaemia, and skin infections (predominantly cellulitis). There is no evidence for an increased incidence of cataract or diverticulitis in PMO patients (their inclusion in this statement reflects observations in prostate cancer patients).	Comment noted. Section 2.2 of the FAD has been updated to reflect the summary of product characteristics.
Amgen	Section 2.2 states: For full details of side effects and contraindications, see the summary of product characteristics. The correct terminology should be adverse events rather than side effects. Proposed text: For full details of adverse events and contraindications, see the summary of product characteristics.	Comment noted. Section 2.2 of the FAD has been updated to state 'adverse events'.

Amgen	Section 3.4 states: No significant differences were seen between treatment groups in measures of health-related quality of life at baseline compared with year 3, or when comparing women without any fractures with women with incident clinical fractures. Decreases in scores for 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 $p < 0.0001$). This should be split into two sentences and restructured as currently there is room for misinterpretation of the text. Proposed text: There were no significant differences between treatment groups in health-related quality of life measures when comparing baseline with year 3. Compared with women without any fractures, women with incident clinical fractures, regardless of treatment group, reported declines in two OPAQ-SV dimensions (physical function and emotional status) and in EQ-5D health index and visual analogue scale scores (all $p < 0.001$; Table B10) at year 3.	Details about the decline in OPAQ-SV scores are not included in the FAD. Please see section 3.4 of the FAD.

Amgen	Section 3.5 states: 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 women receiving denosumab compared with one woman receiving placebo (p = 0.002). We suggest the text “Only one serious adverse effect of denosumab was reported in the FREEDOM study” is amended to be more precise. There were no significant differences between subjects who received denosumab and those who received placebo in the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events. Twelve subjects (0.3%) in the denosumab group reported serious adverse events of cellulitis (including erysipelas), compared with one subject (<0.1%) in the placebo group (P = 0.002). There were no significant differences in the overall incidence of adverse events of cellulitis, with 47 (1.2%) in the denosumab group and 36 (0.9%) in the placebo group. Proposed text: There were no significant differences in the FREEDOM study between subjects who received denosumab and those who received placebo in the total incidences of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events. Only one serious adverse effect of denosumab was observed which had a statistically significant difference^ which was noted in skin infections occurred in 12 women receiving denosumab (0.3%) compared with one woman receiving placebo (<0.1%) (p = 0.002). ^ To adjust for multiple comparisons for numerous reports of adverse events, it was specified in advance to report MedDRA preferred terms of serious adverse events that occurred in at least 0.1% of subjects in either group with a P value of 0.01 or less.	Comment noted. Section 3.5 has been updated to state ‘A statistically significant difference was noted in skin infections, which occurred in 12 women receiving denosumab compared with one woman receiving placebo (p = 0.002)’.

Amgen	3.5 (and Section 4.2.1 of ERG report, p32) states: However, when all studies of denosumab were pooled in a meta-analysis by the manufacturer, no statistically significant difference in adverse effects was observed. This text is inaccurate as statistical tests were not performed; only numbers and percentages were reported. When the four pivotal trials (20030216 [FREEDOM], 20040132 [DEFEND], 20040135 [HALT], and 20040138) were pooled in the combined safety analysis set, the small differences (i.e., ≤ 0.5% higher in the denosumab group) noted in individual studies in certain serious adverse events (e.g., cellulitis and erysipelas in trial 20030216 [FREEDOM] or diverticulitis in trial 20040138) were not evident (i.e., combined incidences of cellulitis: 0.2% denosumab, 0.1% placebo; erysipelas: 0.2% denosumab, < 0.1% placebo; and diverticulitis: 0.3% denosumab, 0.1% placebo). Proposed text: However, when all studies of denosumab were pooled in a meta-analysis by the manufacturer, no notable difference in adverse events was observed.	Section 3.5 of the FAD states that 'overall incidences of adverse events, serious adverse events and adverse events leading to treatment withdrawal were generally similar between denosumab and placebo groups'.
Amgen	Section 3.6 states: Given the wide availability of generic bisphosphonates, denosumab was expected to be an option for women in whom oral bisphosphonates are unsuitable. The text is imprecise. We have provided suggested text to improve clarity. Proposed text: Given the wide availability of generic oral bisphosphonates in the UK, denosumab was expected to be an option for women in whom oral bisphosphonates are unsuitable.	Comment noted. Sections 3.6, 3.7, 3.9, and 3.38 of the FAD state 'oral bisphosphonates'.
Amgen	Section 3.7. states: …reasons for unsuitability are that the woman is unable to comply with the special instructions for the administration of bisphosphonates, or has a contraindication to or is intolerant of bisphosphonates. The current wording is inconsistent with the wording directly above, and could lead to misinterpretation of the eligible patient population. Proposed text: …reasons for unsuitability are that the woman is unable to comply with the special instructions for the administration of oral bisphosphonates, or has a contraindication to or is intolerant of oral bisphosphonates.	Comment noted. Sections 3.6, 3.7, 3.9, and 3.38 of the FAD state 'oral bisphosphonates'.

Amgen	Section 3.8 states: The manufacturer's submission stated that the percentage of patients discontinuing treatment with oral bisphosphonates within 1 year is at least 42% and the median duration of treatment with oral bisphosphonates has been estimated to be 1.2 years. We propose this text be amended to be more precise. Proposed text: The manufacturer's submission stated that the percentage of patients discontinuing treatment with oral bisphosphonates within 1 year is at least 42% and the median duration of treatment with oral bisphosphonates has been estimated to be as low as 1.2 years.	Comment noted. Section 3.8 of the FAD states 'as low as 1.2 years'.
Amgen	Section 3.9 states: The first investigated the primary prevention of fragility fractures in women (70 years and over) with osteoporosis (T-score of −2.5 SD or below) who are unable to comply with the special instructions for the administration of bisphosphonates, or have a contraindication to or are intolerant of bisphosphonates. The second investigated the secondary prevention of subsequent fragility fractures in women (70 years and over) with osteoporosis (T-scores of −2.5 SD or below) and prior fragility fractures who are unable to comply with the special instructions for the administration of bisphosphonates, or have a contraindication to or are intolerant of bisphosphonates. As in Section 3.7, text improvements are suggested to improve the clarity of the ACD. Proposed text: The first investigated the primary prevention of fragility fractures in women (70 years and over) with osteoporosis (T-score of 2.5 SD or below) who are unable to comply with the special instructions for the administration of oral bisphosphonates, or have a contraindication to or are intolerant of oral bisphosphonates. The second investigated the secondary prevention of subsequent fragility fractures in women (70 years and over) with osteoporosis (T-scores of 2.5 SD or below) and prior fragility fractures who are unable to comply with the special instructions for the administration of oral bisphosphonates, or have a contraindication to or are intolerant of oral bisphosphonates.	Comment noted. Sections 3.6, 3.7, 3.9, and 3.38 of the FAD state 'oral bisphosphonates'.

Amgen	3.15 (and Section 3.31 in ERG report, p22 states: Persistence and compliance were assumed to be 100% for the 5-year treatment period for all modelled treatments. Sensitivity analysis was carried out for oral therapies only. This is incorrect. In Amgen's restructured submission (dated 15 February 2010), we explain how the persistence with denosumab had been varied (see Section 6.2.8 pp 170-171 in the submission). This was also pointed out in Amgen's letter dated 31 March 2010 addressing factual inaccuracies in the ERG report. Proposed text: Persistence and compliance were assumed to be 100% for the 5-year treatment period for all modelled treatments. Sensitivity analysis was carried out for oral therapies and for denosumab	Comment noted. Section 3.15 of the FAD states that sensitivity analysis was carried out for oral therapies and denosumab
Amgen	Section 3.23 states: Following a request from the ERG, 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. The additional analysis referred to was in fact carried out by the ERG in developing their report (see Section 6 of the ERG Report, 'Additional work carried out by the ERG'). Proposed text: The ERG performed an analysis in which the cost of administering denosumab was increased, to assess cost-effectiveness if it were delivered in secondary care.	Comment noted. This section has been reworded slightly. The analysis referred to was presented in Table B74, page 256 of Amgen's submission. Please see FAD section 3.22.

Amgen	Section 3.28 states: The ERG identified several problems with the manufacturer's economic model, specifically: • the choice of comparator • cost assumptions for denosumab • the validity of assumptions used for modelling utilities, costs, persistence and compliance • variations in 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. These were aspects of the economic analysis which the ERG identified as needing additional investigation, but were not "problems with the manufacturer's economic model". • The choice of comparator was verified by the Appraisal Committee; there was no problem with the model in this respect. The comparators that the Appraisal Committee concluded were relevant in Section 4.3 of the ACD (strontium ranelate and raloxifene) were included as primary comparators in Amgen's restructured submission (dated 15 February 2010).; interventions that the Appraisal Committee concluded were potential comparators (zoledronate and teriparatide) were included as secondary comparators in Amgen's restructured submission (dated 15 February 2010). • Assumptions used for modelling the cost of denosumab (including treatment setting and administration costs), utilities, costs, persistence, and compliance were all explored in Amgen's restructured submission (dated 15 February 2010).. • Variations in cost-effectiveness in subgroups were explored in Amgen's restructured submission (dated 15 February 2010).	Comment noted. Section 3.28 has been reworded to 'The ERG identified several issues'.

Amgen	• Regarding omission of underlying fracture risk estimates from the probabilistic sensitivity analysis see page 2 of this document • In Section 4.14 of the ACD, the Appraisal Committee concluded that it is likely that treatment with denosumab will be started in secondary care and subsequently delivered in primary care, but with follow-up of women with severe osteoporosis in secondary care in accordance with current UK clinical practice. Proposed text: The ERG identified several aspects of the manufacturer's economic analysis which in their opinion required additional investigation, specifically: • the choice of comparator • cost assumptions for denosumab • the validity of assumptions used for modelling utilities, costs, persistence and compliance • variations in 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.	
Amgen	Section 3.31 states: However, the effect of these assumptions on the cost-effectiveness estimates was unclear. Amgen believes that the direction of the effect is clear, although the extent of the effect is not entirely clear. Proposed text: These assumptions would favour less efficacious therapies; however, the extent of the effect on the cost-effectiveness estimates remains unclear.	Comment noted. Section 3.31 of the FAD states that the extent of the effect of the assumptions on the cost effectiveness estimates was unclear.
Amgen	3.32 (and Section 3.31 in ERG report, p22 states: The manufacturer carried out sensitivity analyses that examined variations in persistence for oral therapies, but variation in persistence with denosumab was not examined. As pointed out in Amgen's letter dated 31 March 2010 addressing factual inaccuracies in the ERG report, Amgen conducted these analyses including denosumab. (See: Amgen's restructured submission, dated 15 February 2010, Section 6.2.8 pp 170-171). Proposed text: The manufacturer carried out sensitivity analyses that examined variations in persistence for oral therapies and for denosumab.	Comment noted. Section 3.33 of the FAD states that the manufacturer carried out sensitivity analyses that examined variations in persistence for oral therapies and denosumab.

Amgen	Section 3.34 states: Based on the assumptions in the manufacturer's base-case analysis, a comparison of denosumab with oral bisphosphonates carried out by the ERG suggested that denosumab may be a cost-effective option for women who cannot take alendronate (ICERs of £21,189 per QALY gained compared with risedronate and £8680 per QALY gained 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 SD). Therefore, for women who cannot take oral alendronate, denosumab might be considered cost-effective compared with risedronate and/or oral ibandronate. This analysis was in fact carried out by Amgen and was reported in Appendix 15 of Amgen's restructured submission (dated 15 February 2010; Tables B71c through B73c). The ERG did not conduct this analysis. Proposed text: Based on a comparison of denosumab with oral bisphosphonates carried out by the manufacturer, the ERG suggested that denosumab may be a cost-effective option for women who cannot take alendronate (ICERs of £21,189 per QALY gained compared with risedronate and £8680 per QALY gained compared with oral ibandronate in the lower risk cohort – that is, a 70-year-old women with no prior fragility fracture and a T-score of −2.5 SD). Therefore, for women who cannot take oral alendronate, denosumab might be considered cost-effective compared with risedronate and/or oral ibandronate.	Comment noted. These details are not included in the FAD.
Amgen	3.37 (and Section 2.2 of ERG report, p15) states: The oldest age groups also have the highest proportion of women treated with bisphosphonates, and it is for these groups that the manufacturer expects denosumab to be an alternative treatment. As noted earlier in regard to Section 3.7, the GPRD analysis did not include IV bisphosphonates. Please update text to ensure clarity. Proposed text: The oldest age groups also have the highest proportion of women treated with oral bisphosphonates, and it is for these groups that the manufacturer expects denosumab to be an alternative treatment.	Comment noted. Sections 3.6, 3.7, 3.9, 3.38, and 4.3 of the FAD state 'oral bisphosphonates'.

Amgen	Section 4.3 states: The Committee heard from the clinical specialists that current UK clinical practice is to start treatment with oral bisphosphonates, but that these are not suitable for all women (reasons for unsuitability are that the woman is unable to comply with the special instructions for the administration of bisphosphonates, or has a contraindication to or is intolerant of bisphosphonates). As noted earlier in regard to Section 3.7, text improvements are suggested to improve the clarity of the ACD. Proposed text: The Committee heard from the clinical specialists that current UK clinical practice is to start treatment with oral bisphosphonates, but that these are not suitable for all women (reasons for unsuitability are that the woman is unable to comply with the special instructions for the administration of oral bisphosphonates, or has a contraindication to or is intolerant of oral bisphosphonates).	Comment noted. Sections 3.6, 3.7, 3.9, 3.38, 4.3, and 4.18 of the FAD state 'oral bisphosphonates'.
Amgen	Section 3.3 states: The manufacturer stated that denosumab was not expected to compete with oral bisphosphonates in clinical practice, given the wide availability of generic bisphosphonates in the UK. As noted earlier in regard to Section 3.7, text improvements are suggested to improve the clarity of the ACD. Proposed text: The manufacturer stated that denosumab was not expected to compete with oral bisphosphonates in clinical practice, given the wide availability of generic oral bisphosphonates in the UK.	Comment noted. Sections 3.6, 3.7, 3.9, and 3.38 of the FAD state 'oral bisphosphonates'. Please see FAD section 3.6.
Amgen	Section 4.4 states: The Committee also noted that manufacturer did provide an analysis of denosumab compared with oral bisphosphonates for completeness. There appears to be a missing word. Proposed text: The Committee also noted that the manufacturer did provide an analysis of denosumab compared with oral bisphosphonates for completeness.	Comment noted. Please see section 4.4 of the FAD.

Amgen	Section 4.9 states: The Committee noted that studies of denosumab for other indications have shown that treatment may be associated with osteonecrosis of the jaw, but it was satisfied with the clinical specialists' views that there was no evidence of this from the clinical studies of denosumab in women with osteoporosis. Subsequent to our evidence submission, positively adjudicated osteonecrosis of the jaw (ONJ) was observed in study 20060289, the open label extension to the FREEDOM study. The final approved SPC dated 26th May 2010 section 4.8 now includes the following text. "In the osteoporosis clinical trial program (8710 patients treated 1 year), ONJ was reported rarely with Prolia." Proposed text: The Committee noted that studies of denosumab in osteoporosis have shown that treatment may be rarely associated with osteonecrosis of the jaw.	Comment noted.
Amgen	Section 4.10 states: However, the Committee was mindful of the ERG's concerns about a number of aspects of the economic model, such as the long-term effects of fractures on mortality, the setting where denosumab is likely to be given, and the associated administration and monitoring costs modelled. The Appraisal Committee concluded that with the exception of administration costs for denosumab, alterations to most key parameters had limited impact on comparisons between denosumab and the primary and secondary comparators. Proposed text: However, the Committee was mindful of the ERG's concerns about a number of aspects of the economic model, such as the long-term effects of fractures on mortality, the setting where denosumab is likely to be given, and the associated administration and monitoring costs modelled. The Committee concluded that with the exception of administration costs for denosumab, alterations to most key parameters had limited impact on comparisons between denosumab and the primary and secondary comparators.	Comment noted.

Amgen	Section 4.13 states: When the manufacturer increased the cost of administering denosumab (by assuming that it would be delivered in secondary care), this increased the ICER for denosumab compared with no treatment from £29,200 to £36,200 per QALY gained for primary prevention, and from £12,400 to £15,700 per QALY gained for secondary prevention. This analysis assumed one administration per year in secondary care. Earlier in the ACD, absolute rather than rounded figures have been used. These have been corrected here for consistency. Proposed text: When the manufacturer increased the cost of administering denosumab (by assuming that one administration per year would be delivered in secondary care), this increased the ICER for denosumab compared with no treatment from £29,233 to £36,185 per QALY gained for primary prevention, and from £12,381 to £15,720 per QALY gained for secondary prevention.	Comment noted. Please note that in the considerations section of the guidance, it standard for rounded figures to be reported for ICERs. .
Amgen	Section 4.16 states: The Committee concluded that for the primary prevention of osteoporotic fragility fractures, denosumab was a cost-effective use of NHS resources as a treatment option only for postmenopausal women at increased risk of fractures for whom oral bisphosphonates are unsuitable (as described above), and who have the same level of fracture risk as described in the recommendations of NICE technology appraisal 160 for strontium ranelate. The bolding of the text is not easy to understand, or is incomplete. We suggest either removing it or amending it. Proposed text: The Committee concluded that for the primary prevention of osteoporotic fragility fractures, denosumab was a cost-effective use of NHS resources as a treatment option only for postmenopausal women at increased risk of fractures for whom oral bisphosphonates are unsuitable (as described above) and who have the same level of fracture risk as described in the recommendations of NICE technology appraisal 160 for strontium ranelate.	Comment noted. Please note that the ACD contained a formatting error. Section 4.16 of the FAD does not include bold text.

Amgen	Section 4.17 states: The Committee noted that the ICER for denosumab compared with no treatment was £29,200 per QALY gained in the manufacturer's base-case analysis, and this increased to £40,600 per QALY gained in the ERG's additional analyses. Earlier in the ACD, absolute rather than rounded figures have been used. These have been corrected here for consistency. Proposed text: The Committee noted that the ICER for denosumab compared with no treatment was £29,233 per QALY gained in the manufacturer's base-case analysis, and this increased to £40,627 per QALY gained in the ERG's additional analyses.	Comment noted. Please note that in the considerations section of the guidance, it standard for rounded figures to be reported for ICERs.
Amgen	Section 4.17 states: The ICERs for denosumab compared with no treatment from the manufacturers model varied between £19,300 and £71,300 per QALY gained. Earlier in the ACD, absolute rather than rounded figures have been used. These have been corrected here for consistency. Proposed text: The ICERs for denosumab compared with no treatment from the manufacturer's model varied between £19,313 and £71,319 per QALY gained.	Comment noted. Please note that in the considerations section of the guidance, it standard for rounded figures to be reported for ICERs..

Amgen	Section 4.18 states: For the secondary prevention of osteoporotic fragility fractures, the Committee noted that the ICER for denosumab compared with no treatment in women for whom oral bisphosphonates are unsuitable was £12,400 per QALY gained in the manufacturer's base-case analysis, which increased to £17,900 per QALY gained in the ERG's additional analyses. Denosumab dominated raloxifene or had an ICER of £2000 per QALY gained in the manufacturer's base-case analysis, which increased to £12,200 per QALY gained in the ERG's additional analyses. The cost-effectiveness results for denosumab compared with strontium ranelate ranged from strontium ranelate being dominated by denosumab in the manufacturer's base-case analysis to an ICER of £6600 per QALY gained in the ERG's additional analyses. Earlier in the ACD, absolute rather than rounded figures have been used. These have been corrected here for consistency. Proposed text: For the secondary prevention of osteoporotic fragility fractures, the Committee noted that the ICER for denosumab compared with no treatment in women for whom oral bisphosphonates are unsuitable was £12,381 per QALY gained in the manufacturer's base-case analysis, which increased to £17,851 per QALY gained in the ERG's additional analyses. Denosumab dominated raloxifene or had an ICER of £2,046 per QALY gained in the manufacturer's base-case analysis, which increased to £12,171 per QALY gained in the ERG's additional analyses. The cost-effectiveness results for denosumab compared with strontium ranelate ranged from strontium ranelate being dominated by denosumab in the manufacturer's base-case analysis to an ICER of £6,606 per QALY gained in the ERG's additional analyses.	Comment noted. Please note that in the considerations section of the guidance, it standard for rounded figures to be reported for ICERs.

Amgen	Section 4.18 states: The Committee also noted the results of the subgroup analysis by age and T-score for women for whom bisphosphonates are unsuitable (as described above) and in circumstances where none of the treatments that have been appraised by NICE are recommended, in which the ICER for denosumab compared with no treatment varied between £12,289 and £22,957 per QALY gained. As noted earlier in regard to Section 3.7, text improvements are suggested to improve the clarity of the ACD. Proposed text: The Committee also noted the results of the subgroup analysis by age and T-score for women for whom oral bisphosphonates are unsuitable (as described above) and in circumstances where none of the treatments that have been appraised by NICE are recommended, in which the ICER for denosumab compared with no treatment varied between £12,289 and £22,957 per QALY gained.	Comment noted. Sections 3.6, 3.7, 3.9, 3.38, 4.3, and 4.18 of the FAD state 'oral bisphosphonates'.

Amgen	**Summary of comments on Summary of Appraisal Committee's Key Conclusions** *What is the position of the treatment in the pathway of care for the condition?* Current text: The Committee noted that the manufacturer's decision problem focused on postmenopausal women diagnosed with osteoporosis for whom oral bisphosphonates are unsuitable, and that the manufacturer stated that denosumab was not expected to compete with oral bisphosphonates in clinical practice, given the wide availability of generic bisphosphonates in the UK. The Committee also noted that manufacturer did provide an analysis of denosumab compared with oral bisphosphonates for completeness. It accepted that is was reasonable to base its considerations on women for whom oral bisphosphonates are unsuitable and the subsequent discussion focussed on this population only. Comments: See comments regarding Section 4.4. on inclusion of the word oral in the text to make it more explicit, and also missing word 'the'. Proposed text: The Committee noted that the manufacturer's decision problem focused on postmenopausal women diagnosed with osteoporosis for whom oral bisphosphonates are unsuitable, and that the manufacturer stated that denosumab was not expected to compete with oral bisphosphonates in clinical practice, given the wide availability of generic oral bisphosphonates in the UK. The Committee also noted that the manufacturer did provide an analysis of denosumab compared with oral bisphosphonates for completeness. It accepted that is was reasonable to base its considerations on women for whom oral bisphosphonates are unsuitable, and the subsequent discussion focussed on this population only. *Adverse effects:* Current text: The Committee concluded that the available clinical evidence on the adverse effects associated with denosumab indicated that it was a well tolerated treatment for the prevention of osteoporotic fragility fractures in postmenopausal women. Comments: The correct terminology should be adverse events rather than adverse effects Proposed text: The Committee concluded that the available clinical evidence on the adverse events associated with denosumab indicated that it was a well-tolerated treatment for the prevention of osteoporotic fragility fractures in postmenopausal women.	Comment noted. Sections 3.6, 3.7, 3.9, 3.38, 4.3, and 4.18 of the FAD state 'oral bisphosphonates'. Comment noted. Summary table has been updated to state adverse events.

Amgen	*Are there specific groups of people for whom the technology is particularly cost-effective?* Current text: …as indicated in the following table'. Comments The table has been omitted Proposed action: Please include the missing table. *Most likely cost-effectiveness estimate (given as an ICER)* Current text: Denosumab dominated raloxifene or had an ICER of £2000 per QALY gained (age 70, T-score -2.5) in the manufacturer's base-case analysis, which increased to £12,200 per QALY gained in the ERG's additional analyses. Comments The wording here is unclear. In the Amgen base case, the ICER versus raloxifene was £2,046. It is not clear why the wording 'dominated raloxifene or' has been included. Proposed text: Denosumab had an ICER of £2,046 versus raloxifene per QALY gained (age 70, T-score 2.5) in the manufacturer's base-case analysis, which increased to £12,200 per QALY gained in the ERG's additional analyses.	Please note that the ACD contained a formatting error. Please see the FAD summary table. Comment noted. In the manufacturer's subgroup analyses (table B87 of the manufacturer's submission) the cost effectiveness estimates ranged from denosumab dominating raloxifene to having an ICER of £2000 per QALY gained (at age 70, T-score -2.5).
Amgen	**Implementation:** *Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* Amgen considers that the provisional recommendations are a sound and suitable basis for guidance to the NHS. *Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?* Amgen does not believe that there are equality-related issues needing special consideration which have not been highlighted in previous submissions and consultations.	Comment noted. Comment noted.

National Osteoporosis Society	*Has all of the relevant evidence been taken into account?* The evidence considered is relevant and appropriate comparators are used. *Are summaries of the clinical and cost effectiveness evidence reasonable interpretations of the evidence?* We feel that the interpretation fo clinical and cost effectiveness are reasonable. We concur with the view of the Committee that the provision of denosumab in primary care will probably lie outside the General Medical Services contract and may require some additional funding via a Locally Enhanced Service (LES) payment. However, the costs of administering the treatment are likely to remain low, even under these circumstances. *Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* The recommendations are clear, straightforward and explain how the use of denosumab should fit in the with the existing Technology Appraisals for osteoporosis treatments (TA160/TA161). It is our view that the clarity of the recommendations facilitates their adoption into NHS practice. *Are there any aspects of the recommendations that need particular consideration to ensure that we avoid unlawful discrimination against any group of people on the ground of gender, race, disability, age, sexual orientation, religion or belief?* We have no specific comments. I would like to note that there are issues within this document (e.g. clinical practice moving towards fracture risk assessment rather than T-score thresholds) which are common with Ta160 and TA161 and that the National Osteoporosis Society is in ongoing discussions with NICE to resolve. As these matters are being dealt with by other means, I have decided not to raise these separately in this response.	Comment noted. Comment noted. Comment noted. Comment noted.

Royal College of Nursing	*i) Has the relevant evidence been taken into account?* This seems comprehensive and we are not aware of any new information that should be considered. *ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?* The summaries seem reasonable interpretations of the evidence. The preliminary views on the resource impact and implications for the NHS seem appropriate. *iii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?* The provisional recommendations of the Appraisal Committee appear suitable basis for preparation of guidance to the NHS. *iv) Are there any equality related issues that need special consideration that are not covered in the ACD?* None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	 Comment noted. Comment noted. Comment noted. Comment noted. Please see section 4.26 of the FAD.

Society for endocrinology	*i) Has the relevant evidence been taken into account?* Yes *ii) Are the summaries of clinical and cost effectiveness reasonable* I recognise that the relevance of persistence and compliance has quite rightly been included in the manufacturer's cost effectiveness modelling. These variables cannot be underestimated in real world use. It is less clear however whether NICE has factored in such variables in their modelling and how much weight these variables carry. Could this be clarified please? *iii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?* No. Lack of a clinical guideline to support the real world clinical use of this information makes it practically very difficult to deliver NICE guidance in the NHS. It is not tenable for patients to be eligible for generic alendronate, be intolerant to it and then be informed there is no seamless link to the next available drug. There is a perception that the patient's condition would have to 'deteriorate' in terms of BMD or CRFs before next level treatment (denosumab in this instance) can be prescribed. A clinical guideline is required to effectively 'join up' management of real world patients with osteoporosis and high fracture risk. *iv) Are there any equality related issues that need special consideration that are not covered in the ACD?* Yes. There is mention that older people may have problems administering s/c injections. I am concerned that this is an over-generalisation and in real world experience of usage of s/c anabolic drugs (e.g. teriparatide), patients with visual failure and patients with rheumatoid disease, who are perceived to have poor dexterity, have managed their (daily in the case of teriparatide) injections admirably.	Comment noted. Comment noted. Please see section 4.5 of the FAD. Comment noted. The NICE clinical guideline on osteoporosis is currently suspended until further notice. Comment noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
British Society for Rheumatology	I have one main comment on the appraisal, concerning the primary prevention indication. I agree with the idea of trying to set a threshold of fracture risk for use of denosumab in primary prevention. However, using the table from NICE TAG 160 concerning strontium is to my mind not really an option given the recent successful appeal by strontium which has forced NICE to drop this. I can understand the desire to be consistent with TAG 160, in which case there might be a case for using another table eg that relating to risedronate. Having said that, the various risk factor tables included in TAG 160 have not been widely taken up in clinical practice, and in my view a better option would be to use a ten year fracture risk cut-off as calculated by the WHO frax tool.	Comment noted. The Committee was not persuaded that recommendations about treatment should be based on absolute risk as calculated using FRAX and that the stepped approach of assessing fracture risk is required to ensure the effective allocation of NHS resources. The Committee concluded that using a combination of T score, age and a number of independent clinical risk factors for fracture remained more appropriate for defining treatment recommendations in this appraisal. Please see FAD section 4.15 of the FAD.

Nominating organisation	Comment	Response
National Osteoporosis Society	*i) Has the relevant evidence been taken into account?* Yes	Comment noted.
	ii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? Yes, but I agree with the Expert Review Group that it is unlikely that the administration of denosumab will be provided in primary care as part of General Medical Services. This may therefore require additional funding as a Locally Enhanced Service, but the costs are likely to be modest.	Comment noted.
	iii) Are there any equality related issues that need special consideration that are not covered in the ACD? I welcome the Appraisal Committee's recommendations on the use of denosumab for the secondary prevention of fragility fractures, which will allow postmenopausal women at increased risk of fractures to gain access to effective treatment for osteoporosis, if they are unable to take or tolerate oral bisphosphonates. Although the Committee's preliminary recommendations on the use of denosumab for the primary prevention of fragility fractures follow the approach adopted for second line agents in Technology Appraisal (TA) 160, I feel that the use of age, T-Scores and number of clinical risk factors for fracture, rather than absolute risk of fracture calculated by FRAX□, may be difficult to use in clinical practice. Furthermore, as with TA 160 and TA 161, some women who meet the criteria for treatment with generic alendronate, but are unable to take or tolerate this medication, will need to lose bone before qualifying for treatment with denosumab or an alternative agent. This is a difficult situation for a clinician to explain and justify to a patient.	Comment noted. Comment noted. The Committee was not persuaded that recommendations about treatment should be based on absolute risk as calculated using FRAX and that the stepped approach of assessing fracture risk is required to ensure the effective allocation of NHS resources. The Committee concluded that using a combination of T score, age and a number of independent clinical risk factors for fracture remained more appropriate for defining treatment recommendations in this appraisal. Please see FAD section 4.15 of the FAD.
	iv) Are the summaries of clinical and cost effectiveness reasonable The one area of potential discrimination is the situation of primary prevention in a postmenopausal woman with swallowing problems as a result of disabling stroke disease, who is otherwise eligible for treatment with oral alendronate, but does not fulfill the criteria for denosumab or other treatments.	Comment noted. Please see FAD section 4.26.

Comments received from commentators

Commentator	Comment	Response
Novartis	1. <u>UK List Price of Zoledronic acid (Zoledronate) 5 mg (Aclasta®)</u> The manufacturer's submission cites the UK list price for zoledronate 5 mg as £283.74 (Table B63, column entitled "mean cost per year", p228). This was correct until the price for zoledronate 5 mg was reduced on 1st January 2010. Since this date, the cost per vial of zoledronate 5 mg has been £266.72. The manufacturer's submission is dated 15th January, after the price cut was effective, although we acknowledge that publicly available sources of cost information are unlikely to have been updated by this time. The new price does not appear to have been picked up by the manufacturer, the ERG or NICE. The source for drug costs in the manufacturer's submission is the British National Formulary (BNF) September 2009, although we are conscious that the BNF is only updated every 6 months and has a long lead time for updates. This is because it takes the bulk of its pricing data from NHSBS prescription services via the DM+D service (http://dmd.medicines.or.uk) (for example, although communicated to BNF in January 2010, the price change for zoledronate 5 mg will not be reflected in the BNF until publication of BNF 60 in September 2010). Therefore, the BNF is sometimes not the most appropriate source of UK drug cost information for economic evaluations. Cross checking prices with other accepted sources of information for drug costs should have identified the price change prior to the finalisation of the ERG report (dated 23rd March 2010) and the Appraisal Committee meeting (which took place on 27th April 2010). For example, the updated price of £266.72 has appeared in the Monthly Index of Medical Specialities (MIMS) since February 2010.	Comment noted. The ERG was requested to carry out exploratory analyses which showed that denosumab was less effective and less costly than zoledronate. The Committee had already concluded that although treatment with denosumab may be started in secondary care, it will be subsequently delivered almost exclusively in primary care, unlike the administration of zoledronate, use of which will remain in a secondary care setting. As the Committee regarded the main comparators for denosumab to be those treatments delivered in primary care when oral bisphosphonates were unsuitable (no treatment, strontium ranelate, raloxifene), it did not regard these issues to be central to the decision problem. Please see FAD section 4.18.

Commentator	Comment	Response
Novartis	2. Wrist Fracture Relative Risk (RR) for Zoledronate • "None of the treatments were associated with a statistically significant decrease in the risk of wrist fracture (RR of 0.84 for denosumab, 0.98 for strontium ranelate and 0.29 for teriparatide; no data were available for zoledronate or raloxifene)" (ACD point 3.7, p9)..... • "the relative risk for interventions where data for wrist and hip fractures were not available was assumed to be 1.00" (ACD point 3.13, p13) The above statements suggest that the manufacturer's systematic review did not locate any wrist fracture data for zoledronate. Table B21 of the manufacturer's submission (p106-8) indicates that the efficacy data from one study, HORIZON-PFT (Black et al. 2007) provided relative risks (RRs) for zoledronate in the manufacturer's model. This table also confirms that Black et al. (2007) did not report a wrist fracture RR. However, not reporting results at a specific fracture site cannot be interpreted as a complete lack of efficacy at that site. We note that the ERG agreed that this assumption was unreasonable and performed an analysis in which the risk reduction for zoledronate at the wrist was set to 15.8% (i.e. they used the RR of 0.84 reported RR for denosumab). The list of articles excluded in the manufacturer's systematic review is not provided in the Evaluation Report. However, it is reasonable to expect that a number of articles reporting results from the HORIZON-PFT study (e.g. congress abstracts) were excluded on the basis that they were secondary publications. One of these congress abstracts (Black et al. 2009) reports the effect of zoledronate on a subset of six non-vertebral fractures (wrist, hip, pelvis, humerus, leg and clavicle). Although the abstract only reports fracture reductions at an aggregated level across all six sites, the poster presentation reports the RRs at each fracture site individually. The poster is attached separately and highlights a RR of 0.81 (95% CI 0.62-1.06) (p=ns) for zoledronate at the wrist. This RR is considerably lower than the RR applied by the manufacturer in their model (1.0) and also lower than the denosumab RR (0.84) applied by the ERG to equalise the wrist RRs for the zoledronate vs. denosumab comparison. We agree with the ERG that it is unreasonable to assume an RR of 1.0 for zoledronate at the wrist based on "lack of evidence" and suggest that the evidence-based RR of 0.81 is used in any future analyses considered by the Appraisal Committee.	Comment noted. The ERG was requested to carry out exploratory analyses which showed that denosumab was less effective and less costly than zoledronate. The Committee had already concluded that although treatment with denosumab may be started in secondary care, it will be subsequently delivered almost exclusively in primary care, unlike the administration of zoledronate, use of which will remain in a secondary care setting. As the Committee regarded the main comparators for denosumab to be those treatments delivered in primary care when oral bisphosphonates were unsuitable (no treatment, strontium ranelate, raloxifene), it did not regard these issues to be central to the decision problem. Please see FAD section 4.18.
Novartis	3. Administration Setting (Primary vs. Secondary Care) and Subsequent Administration Cost	

Commentator	Comment	Response
	There are a number of references to this issue throughout the ACD, for example:- • "Following a request from the ERG, 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 ICER for denosumab compared with no treatment rose to £36,185 per QALY gained in women with no prior fragility fracture, and to £15,720 per QALY gained in women with a prior fragility fracture. This change led to zoledronate dominating denosumab in women with and without a prior fragility fracture." (ACD point 3.23, p17-18) • "When the manufacturer increased the cost of administering denosumab (by assuming that it would be delivered in secondary care), this increased the ICER for denosumab compared with no treatment from £29,200 to £36,200 per QALY gained for primary prevention, and from £12,400 to £15,700 per QALY gained for secondary prevention. The Committee noted that given the similar cost and efficacy of denosumab and zoledronate, changes to this assumption also resulted in zoledronate dominating denosumab for both primary and secondary prevention. However, the Committee was mindful that, although licensed for treatment of osteoporotic fragility fractures, the cost effectiveness of zoledronate has not been appraised by NICE." (ACD Point 4.13, p31-32). Although we are aware of a handful of centres in which zoledronate is administered in primary care settings, we agree with NICE's assessment that zoledronate is mainly used in secondary care in the UK. From the results provided by the manufacturer, it is clear that, in secondary care settings, zoledronate dominates denosumab for primary and secondary prevention. Thus, in patients for whom treatment in secondary care is most appropriate, zoledronate would be the preferred treatment option. The fact that the "cost-effectiveness of zoledronate has not been appraised by NICE" is irrelevant as zoledronate was listed as a comparator in the scope for this appraisal. Zoledronate was reviewed by NICE's Topic Consideration Panel for Long-Term Conditions in March 2007 (NICE 2007); it received a provisional score of 0 (out of 5), with an action specified as follows "NICE to liaise with osteoporosis GDG as necessary to ensure that this topic is included within the guideline." This seemed to signal a welcome move to consolidate recommendations on pharmacological treatment options for osteoporosis. However, the Clinical Guideline on Osteoporosis has never materialised and remains "suspended". <u>Even if NICE cannot make a recommendation for a comparator product within an</u>	Comment noted. Please see FAD sections 4.2 and 4.16. As this is a single technology appraisal (STA), NICE

Commentator	Comment	Response
	STA, we suggest that sections 1.1 and 1.2 provides some clarification for end users of the guidance. An additional statement to reflect that a more clinically effective and cost-effective intravenous treatment option is available for patients receiving their osteoporosis treatment in secondary care settings would be helpful.	can only issue guidance on the use of denosumab in the NHS.
Novartis	4. Duration of Treatment Effect for Denosumab vs. Bisphosphonates We note the following comment in the ACD: "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 women would return in a linear fashion to baseline risk levels over 1 year (a return to baseline levels over the course of 5 years was assumed in NICE technology appraisal guidance 160 and 161)." (ACD Point 3.13, p12). The manufacturer's submission provides no justification for using a 1 year return to baseline risk for all interventions rather than 5 years. The submission makes numerous references to the observation that the effects of denosumab on bone turnover are fully reversible with discontinuation and are restored with subsequent re-treatment. Figure B8 in the manufacturer's submission (p98) illustrates this point and supports the assumption of a rapid return to baseline bone mineral density (BMD) at the lumbar spine, total hip and distal radius in patients treated with denosumab. Thus, a one year return to baseline fracture risk may not be an unreasonable assumption for denosumab. However, figure B8 also illustrates that the return towards baseline BMD levels with alendronate is much more gradual than it is for denosumab. The assessment group model that informed TAs 160 and 161 used a 5 year return to baseline fracture risk concordant with the evidence of this more gradual return to baseline for the available treatments at the time (which included the bisphosphonates alendronate, risedronate and etidronate). In this respect, we note the following comments in the European Public Assessment Report (EPAR) for denosumab (European Medicines Agency, 2010):- • "Within 12 months of discontinuation of denosumab treatment, BMD returned to approximately baseline levels" (EPAR, p33) • "While bisphosphonates bind to the skeleton and are active for several years after discontinuation, denosumab treatment effects disappear within month [sic] after drug discontinuation" (EPAR, p34). Based on this evidence, we suggest that the Appraisal Committee explores the sensitivity of employing a differential timing of return to baseline fracture risk	Comment noted. The Committee heard from the ERG that the duration of benefit in terms of fracture risk (as opposed to bone mineral density) is unknown after cessation of osteoporosis treatments. The Committee concluded that there was little evidence on the duration of effect on fracture risk for osteoporosis treatments and that this was an area of uncertainty. Please see FAD section 4.13.

Commentator	Comment	Response
	according to treatment type i.e. using a 1 year return to baseline for denosumab and a 5 year return to baseline for bisphosphonates as per TAs 160 and 161.	
Novartis	5. Safety and Tolerability There are a number of speculative statements about the safety and tolerability of denosumab in the ACD. For example:- • "The Committee heard from the clinical specialists that denosumab is a monoclonal antibody that reduces osteoclast activity and hence reduces bone breakdown, that it is the first drug of its class, and that its biological mechanism of action results in targeted therapy with fewer adverse events than other treatments." (ACD Point 4.5, p27)" • "The clinical specialists also stated that although denosumab is a biological agent that also has effects on the immune system, it is specifically targeted for regulating bone cells. The clinical specialists therefore felt that the potential safety concerns associated with other biological agents (such as anti-tumour necrosis factors) may not be applicable to denosumab" (ACD Point 4.14, p32). As with any new pharmacological agent with a novel molecular target, the long-term safety implications are uncertain. RANKL is involved in the normal functioning of the immune system and is expressed by activated T cells (Leibbrandt & Penninger, 2008). As acknowledged in the ACD, by targetting RANKL, denosumab also has effects on the immune system in addition to reducing bone resorption. The EPAR for denosumab (European Medicines Agency, 2010) also states that "RANKL inhibition by denosumab theoretically can be linked to an increased incidence of infectious complications and malignancies during denosumab treatment" (EPAR, p41). We suggest that statements in the ACD regarding adverse effects remain factual and evidence-based. If comparisons are made with the adverse event profile of other treatments, it should be made clear whether the comparisons are with other osteoporosis treatments or biological agents for the treatment of other conditions (this particularly applies to point 4.5 from the ACD cited above).	Comment noted.
Servier	1. Strontium ranelate is not an appropriate primary comparator As concluded by the Expert Review Group (ERG) in section 3.29 of the denosumab ACD, Servier asserts that strontium ranelate is not an appropriate primary	Comment noted. The Committee also heard from the clinical specialists that women for whom oral

Commentator	Comment	Response
	comparator for this economic analysis. Zoledronic acid is the natural primary comparator for denosumab by virtue of its similar method of administration (via injection), similar frequency of dosing (yearly vs. 6 monthly) similar place of administration (i.e. a secondary care setting) and similar mode of action of the two treatments (pure antiresorptive effects on the bone through osteoclast inhibition).	bisphosphonates are unsuitable receive either no treatment or strontium ranelate for primary prevention (as set out in NICE technology appraisal guidance 160), or no treatment, strontium ranelate or raloxifene for secondary prevention (as set out in NICE technology appraisal guidance 161). The clinical specialists stated that the management of osteoporosis usually takes place in primary care (both strontium ranelate and raloxifene are given in primary care). Women who have severe osteoporosis may receive more potent agents such as zoledronate or intravenous ibandronate but there is limited capacity for treatment in secondary care because of the need for day-case facilities for these intravenous treatments. The Committee accepted that the great majority of treatment for the primary and secondary prevention of osteoporotic fragility fractures is provided in primary care. It also accepted that women for whom oral therapies are unsuitable or who have severe osteoporosis may receive more potent agents such as zoledronate or intravenous ibandronate in secondary care and that teriparatide is also used for secondary prevention when women are unable to take other therapies. The Committee concluded that the relevant comparators for the primary prevention of osteoporotic fragility fractures are no treatment and strontium ranelate, and the relevant comparators for the secondary prevention of osteoporotic fragility fractures are no treatment, strontium ranelate and raloxifene, as both the administration and supervision of strontium ranelate and raloxifene are organised in primary care. The Committee also concluded that potential comparators for denosumab are zoledronate (for women who have severe osteoporosis) and teriparatide (for women who have sustained a clinically apparent osteoporotic fracture and who are defined by age, T score and number of osteoporotic fractures and

Commentator	Comment	Response
		who are unable to take all oral bisphosphonates, strontium and raloxifene, as defined in NICE Technology Appraisal 161). Please see FAD sections 4.3 and 4.16.
Servier	2. Inappropriate and misleading data has been used in the economic analysis as the point estimate relative risk of hip fracture for strontium ranelate vs. placebo to populate their economic model and make an efficacy comparison. This figure has not been accepted by NICE for the Technology Appraisals 160 & 161 for osteoporosis and hence it cannot be relied upon or deemed acceptable for this analysis or STA. Servier assert the true relative risk of hip fracture in comparison to placebo is 0.64 over 3 years (or 0.57 over 5 years) as accepted by the European Medicines Agency (EMA). The decision by NICE in Technology Appraisals 160 & 161 to reject data submitted by Servier supporting the figure of 0.64, and NICE's conclusion that the correct estimate is 0.85, was recently ruled unlawful by the Court of Appeal NICE on the basis that NICE had failed to give adequate reasons for rejecting that data (and thus for rejecting the estimate of 0.64). A reappraisal of that part of the Technology Appraisals has been ordered by the Court, but currently no figure has been definitively concluded in the reappraisal. The figure of 0.89 proposed by the manufacturers of denosumab therefore represents an inaccurate comparison and thus the outputs of their economic analysis cannot be relied upon. In addition, incorrect methodology has been used by the manufacturers of denosumab to calculate the figure of 0.89 as the Relative Risk from the TROPOS 5 year study and hence any economic result based on this figure is misleading, and underestimates the true treatment effect of strontium ranelate. The calculation conducted by the manufacturers of denosumab takes no account of the incidence and differential timing of hip fractures between the strontium ranelate and placebo groups in the TROPOS 5 year study. The most appropriate statistical analysis, described in the TROPOS 5 year study publication, is a Cox proportional hazard model, which corresponds to a comparison of two Kaplan-Meier survival curves and takes into account the time of onset of events and censure. Importantly, adjusting the Relative Risk of hip fracture for strontium ranelate in the economic model, to a figure that reflects its actual efficacy, has significant effects on the overall cost effectiveness in its comparison to denosumab.	Comment noted. The Committee considered the relative risks for hip fracture that were used in the manufacturer's meta-analysis, and that alternative relative risk figures of 0.64 (obtained over 3 years) or 0.57 (obtained over 5 years) for the effect of strontium ranelate on hip fracture were suggested during consultation. Please see section 4.20 of the FAD). The Committee heard from the ERG that exploratory analyses applying the relative risk estimate of 0.64 over the modelled 5-year treatment period in the manufacturer's model resulted in a base case ICER of £10,203 per QALY gained for denosumab compared with strontium ranelate for primary prevention and an ICER of £5052 per QALY gained for secondary prevention. When the relative risk estimate of 0.57 was applied over the modelled 5-year treatment period in the manufacturer's model, this resulted in an ICER of £16,339 per QALY gained for denosumab compared with strontium ranelate for primary prevention and an ICER of £8639 per QALY gained for denosumab compared with strontium ranelate for secondary prevention. The Committee considered these exploratory analyses and concluded that it did not need to make a decision on which relative risk for strontium ranelate was the most appropriate one to apply, because for any of the suggested relative risk values for hip fracture for strontium ranelate, the ICERs for denosumab compared with strontium ranelate fell within a range that was still considered to be a cost effective use

Commentator	Comment	Response
		of NHS resources. Please see section 4.21 of the FAD.
Servier	3. Uncertainty of the true cost effectiveness figure Section 3.24 states “the results of the manufacturer’s probabilistic sensitivity analysis showed that denosumab had an approximately 50% probability of being considered cost effective at a willingness-to-pay threshold of £30,000 per QALY gained compared with the primary comparators (strontium ranelate, raloxifene and no treatment) in the base-case population of women aged 70 years with a T-score at or below −2.5 SD and no prior fracture.” From this result it can be concluded that there is an equal (50%) chance of denosumab showing cost effectiveness or not for primary prevention against primary comparators. Indeed, also in primary prevention, there is only a 60% chance of cost effectiveness being demonstrated against secondary comparators and this further undermines the confidence in the cost effectiveness conclusions for denosumab. When the economic model is subjected to deterministic and sensitivity analysis over plausible ranges, large differences and a wide degree of variability emerges between these results and those used by the manufacturer to argue cost effectiveness (section 3.23). This reduces confidence in the cost effectiveness conclusions derived from the analysis submitted by the manufacturers of denosumab. The model is particularly sensitive to changes in assumptions concerning the place (and therefore cost) of administration of denosumab (section 3.23), argued by the manufacturers to be in primary care and predominantly by patients. The ERG state (section 3.30) that this approach, taken by the manufacturers, has the effect of making the treatment much less costly than what the ERG find is the most appropriate primary comparator, zoledronic acid. As denosumab is likely to be initiated and continued in secondary care, much like zoledronic acid, resource usage for denosumab will therefore be underestimated. In addition, even if denosumab were to be used in primary care the ERG (section 3.36) believe this is unlikely to be part of general medical services but would be provided as an enhanced service requiring additional payment and therefore costs. These have not been accounted for in the initial analysis and could be significantly higher than the manufacturer’s assumption of the average cost of 2 GP visits per year.	Please see sections 4.10 to 4.25 for the Appraisal Committee’s considerations of cost effectiveness evidence. Comment noted. The Committee discussed whether administering denosumab would be part of general medical services or whether it would be regarded as an enhanced service for which an additional payment would be negotiated, and it noted the comments received during consultation on the ACD. The Committee accepted the views of the clinical specialists that there were no specific safety concerns around the use of denosumab and that follow-up in secondary care would not be necessary, and hence it was not persuaded to alter its opinion that denosumab is likely to be provided as part of general medical services in primary care. The Committee concluded that while it may be that treatment with denosumab would be started in secondary care, it would be subsequently delivered almost exclusively in primary care, but with follow-up of the relatively small proportion of women with severe osteoporosis in secondary care continuing in line with current UK clinical practice. Please see section 4.17 of the FAD.

Commentator	Comment	Response
Servier	4. Denosumab does not show quality of life benefits over placebo The FREEDOM study demonstrated no significant difference between the denosumab and placebo arms of the study with respect to health related quality of life outcomes (section 4.12). This is a cause for concern as it could be postulated that any benefits shown with regards to hip fracture rate reduction are offset by a worsening of some other unascertained component of quality of life that is impacting on patients and would therefore impact on overall cost effectiveness. This possibility has not been recognised in the ACD. Section 4.12 states "The Committee heard from the ERG that the number of fracture events with associated EQ-5D scores was low and that there was insufficient information for cross-checking". This is a pivotal point that in our view does not justify the omission of this data from the economic analysis. Considering section 3.10 "when a fracture occurred, women were modelled to remain in the respective fracture state for two cycles (1 year)", it follows therefore that for EQ-5D to be associated with an event it need only be measured within 12 months of the fracture. It is our view that the Committee have been given insufficient information to be persuaded that the manufacturer's approach to modelling Quality of Life was acceptable. Firstly the definition of association (4.12) should be provided to the committee and, secondly, the EQ-5D data should be requested from the manufacturer for the purpose of cross-checking.	Comment noted. Please see section 4.14 of the FAD.

Commentator	Comment	Response
Servier	5. Inappropriate grouping of all oral bisphosphonates with inefficient resource use The Appraisal Committee comment that it is reasonable and acceptable for the manufacturers of denosumab to focus on a population of post menopausal women for whom oral bisphosphonates are unsuitable. This is because the manufacturers claim that denosumab is not expected to compete with oral bisphosphonates. In addition the manufacturers also cite the reason for such a positioning after oral bisphosphonates as the need to make efficient use of UK resources (section 4.4). The ACD guidance therefore indicates denosumab should be used after any oral bisphosphonate for both primary and secondary prevention of fractures. This is quite different and inconsistent with guidance from Technology Appraisals 160 and 161. Here there is clear stratification of the oral bisphosphonates based on cost and clinical factors (e.g. tolerability) and the 3 technologies are not regarded as homogeneous. Technology Appraisals 160 and 161 clearly advocate the use of alendronate first followed by etidronate or risedronate and only after these technologies are alternative treatments recommended. The manufacturer states (section 3.7) that only 6.8% of the current osteoporotic drug use would be eligible for denosumab because this is the percentage of osteoporotic drug use that does not involve oral bisphosphonates. It is claimed this would represent efficient use of UK resources. As the current ACD stands it is likely that denosumab could be used in those patients who cannot take alendronate, which would include the 6.8% of drug use stated above AND at least a further 15.8% (currently the usage of risedronate) because of intolerance to the first oral bisphosphonate. This amount is far greater than what the manufacturers of denosumab have submitted and quite different from the original intention of the guidance; to allocate the use of UK resources efficiently. This current ACD also has the effect of unfairly disadvantaging those technologies appraised in guidance 160/161 who are recommended for use after alendronate, and then either risedronate or etidronate, not just an oral bisphosphonate. Therefore any recommendation for denosumab should follow the stratification developed for non-oral bisphosphonates in guidance 160/161.	Comment noted. The preliminary recommendations in the ACD have been amended. See FAD sections 1.1, 1.2, 4.22 and 4.25.
Servier	Considering the data inaccuracies and lack of confidence in the wide range of cost effectiveness values we believe that the cost effectiveness of denosumab has not been proven against an appropriate comparator. Additionally any guidance should be consistent in positioning and wording with existing NICE osteoporosis guidance TA160/161.	Comment noted. Please see sections 1, 4.3 and 4.16, 4.22 and 4.25 of the FAD.

Commentator	Comment	Response
Warner Chilcott	In section 3.34, the ERG (Evidence Review Group) mentioned that "Based on the assumptions in the manufacturer's base-case analysis, a comparison of denosumab with oral bisphosphonates carried out by the ERG suggested that denosumab may be a cost effective option for women who cannot take alendronate (ICERs of £21,189 per QALY gained compared with risedronate and £8680 per QALY gained 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 SD). Therefore,for women who cannot take oral alendronate, denosumab might be considered cost effective compared with risedronate and/or oral ibandronate" As we have data to the contrary we would be obliged if the following 3 questions can be addressed:- • How does the overall recommendation of the STA fit with TAG 160 & 161 in terms of order of treatment i.e. generic alendronate followed by risedronate or etidronate? • What was the thinking behind classing bisphosphonates all together as this appears not to acknowledge the different efficacy, tolerability and safety profiles? • How was the "ICERs of £21,189 per QALY gained compared with risedronate" derived?	Comment noted. See FAD section 1.1 and 1.2.

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional 1	1	Primary prevention: We note that the T scores for treatment by age and risk factors match those for Strontium in TA 161. However, as denosumab is a biological agent, is likely to be initiated in secondary care and the level of evidence is not as robust as only one trial has patient orientated outcomes we are not clear on the evidence on which this table is based. Also 3 out of the 4 trials in post menopausal women (FREEDOM, DEFEND, STAND) excluded women with a BMD below -4.0, yet these are included in this table. Secondary prevention: There are no criteria for severity of T score or age and risk factors, to decide when it is appropriate to prescribe denosumab other than if an oral bisphosphonate is unsuitable. This is less rigorous than the current guidelines in TA 162 for strontium. We expect denosumab to have a less favourable profile to strontium as it slightly more costly, has to be given by subcutaneous injection and is likely to be initiated in secondary care as it is a new drug. The potential for anaphylactic shock is also greater with parenteral medications. (Subsequent administration may be in primary care setting)	Comment noted. Please see sections 4.15 and 4.22 to 4.25 of the FAD for considerations regarding fracture risk, subgroup analyses and overall conclusions. Comment noted. Please see FAD sections 4.3 and 4.9.
NHS professional 1	2	There is a risk of immunosuppression with denosumab and safety data available is only for 36 months. Â The FDA highlights the slightly increased incidence of serious infection with denosumab, potential increased risk of malignancy and dermatologic side effects as issues for consideration.	Comment noted. Please see FAD section 4.9.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS professional 1	3	We have concerns about the clinical trial evidence for denosumab. Only 1 trial assessed patient orientated outcomes i.e. fracture risk. This was the FREEDOM trial, comparing denosumab versus placebo treatment. Only 1 trial (DECIDE) assessed denosumab against alternative osteoporosis treatment (denosumab versus alendronate) but this used BMD measurement. There are numerous other antiresorptive drugs available generically at a lower cost with evidence of benefit in patient orientated outcomes such as hip fracture. There have been no head to head trials of denosumab against strontium or zoledronic acid which, are suggested as useful comparators. We would question the concluding sentence in paragraph 3.34. Denosumab is more costly than either risedronate or oral ibandronate and does not have the trial data in terms of patient oriented outcomes to support it.	Comment noted. Denosumab is not expected to be an option for women in whom oral bisphosphonates (such as alendronate, risedronate, etidronate) are suitable. Therefore denosumab is not expected to compete with oral bisphosphonates in clinical practice. See FAD section 3.6. The Committee discussed the meta-analysis that was undertaken by the manufacturer to obtain direct estimates for each treatment compared with placebo. However, the Committee noted the lack of a direct comparison of denosumab with active comparators. It was therefore unable to make a conclusion about the relative clinical effectiveness of denosumab, but was satisfied with the evidence on the direct estimates for each treatment compared with placebo and concluded that the methods used in the meta-analysis were sufficiently robust for use in the economic analysis. See FAD section 4.8.

Role*	Section	Comment	Response
NHS professional 1	4	The clinical specialists opinion that the potential safety concerns associated with other biological agents may not be applicable to denosumab cannot be supported by long term safety data at this stage. The ERG considered denosumab (administered in secondary care) as dominating strontium, which is administered in primary care. Strontium is less expensive and in this scenario will not incur the additional secondary care costs. There are no head to head trials of these two drugs in fracture prevention and only one denosumab RCT with patient orientated outcomes so we are not sure how any decisions on comparative effectiveness have been reached. As denosumab is a new biological agent we feel it should be initiated in secondary care. Therefore it should not be considered as an alternative to strontium which can be prescribed and monitored in primary care. We feel that denosumab should only be considered for patients who cannot take oral bisphosphonates or strontium. The re-appraisal of the evidence for efficacy of strontium in hip fractures, may have a bearing on the current conclusions of this appraisal consultation. Denosumab is a cost effective alternative to teriparatide.	Comment noted. Comment noted. The Committee concluded that while it may be that treatment with denosumab would be started in secondary care, it would be subsequently delivered almost exclusively in primary care. For further details please see FAD section 4.17. Comment noted. Please see FAD section 4.20 to 4.25.
NHS professional 1	5	While individual drugs need to be appraised as they become available it would be more useful to know where their place in therapy is, taking into account all other available treatment options. Â It is a concern that an existing osteoporosis treatment option, zolendronic acid, has not been appraised by NICE yet. If a range of drugs are individually approved by NICE without fully determining their place in therapy in comparison to all available options then in order to implement the guidance every PCT will need to duplicate this discussion with local Trusts to manage the clinical and financial risk.	Comment noted. The NICE clinical guideline on osteoporosis is currently suspended until further notice.

Role*	Section	Comment	Response
NHS professional 2	1	The published ACD recommends the use of denosumab for primary as well as secondary prevention. This would have implications for commissioners of postmenopausal osteoporosis services as denosumab (£366 per patient per year) would be used instead of a generic bisphosphonate, eg alendronic acid. The drug is currently recommended for specific clinical subgroups, but commissioners need to consider how they would monitor use in subgroups and prevent broader use. Our Area Prescribing Committee has expressed concern that the number of patients who are non-concordant with alendronate may be large and it would likely be difficult to restrict and audit access.	Comment noted. Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. Comment noted.
NHS professional 2	2	Efficacy in trials has been measured with surrogate markers (bone mineral density), with no demonstrated significant reduction in fractures. Denosumab has been shown to be effective in improving bone mineral density compared with placebo and in the trials comparing denosumab and alendronate, denosumab was more effective in improving bone mineral density. However whilst noting that the STAND and DECIDE trials were not powered to look at fracture risk both demonstrated a greater incidence of fractures in patients receiving denosumab compared to alendronate. Whilst the outcomes in these studies were statistically significant for a greater increase in BMD with denosumab compared to alendronate the clinical significance of these increases is unknown. The treatment has the risk of immunosuppression. Safety has been demonstrated in trials of 36 month duration, but would need further consideration. Patients may be on these drugs for many years and as stated previously the FDA have raised concerns regarding malignancy potential of denosumab. The SPC in America reflects concerns regarding malignancy.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. Comment noted. Please see FAD section 4.9.

Role*	Section	Comment	Response
NHS professional 2	3	Efficacy in trials has been measured with surrogate markers (bone mineral density), with no demonstrated significant reduction in fractures. Denosumab has been shown to be effective in improving bone mineral density compared with placebo and in the trials comparing denosumab and alendronate, denosumab was more effective in improving bone mineral density. However whilst noting that the STAND and DECIDE trials were not powered to look at fracture risk both demonstrated a greater incidence of fractures in patients receiving denosumab compared to alendronate. Whilst the outcomes in these studies were statistically significant for a greater increase in BMD with denosumab compared to alendronate the clinical significance of these increases is unknown.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The manufacturer also carried out a random-effects meta-analysis of the relative risks (RRs) for all fracture endpoints directly comparing each treatment against placebo (denosumab, strontium ranelate, raloxifene, teriparatide and zoledronate). Please see FAD section 3.6. Comment noted. Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments.

Role*	Section	Comment	Response
NHS professional 2	4	There would be an opportunity cost with the use of denosumab in primary prevention. It would likely broaden the cohort of patients receiving medication for post-menopausal osteoporosis to include a group who have concordance issues with alendronate, but where this non-concordance has not been adequately addressed. The use of denosumab in primary prevention was recommended based on ICERs which expect that denosumab would be administered in primary care. Our local primary care clinicians advised that they do not see denosumab as a primary care drug, mainly due to the lack of long term safety data for denosumab, the lack of experience with prescribing ?-mabs? in primary care. Therefore the ICER for primary prevention should be amended accordingly. For women eligible for treatment with teriparatide as per NICE guidance, denosumab is cost effective (slightly less effective but much less costly) for secondary prevention. Therefore use prior to teriparatide may be a cost-effective option but it would likely require additional funding for the osteoporosis care pathway in the long-term if patients ultimately become eligible for teriparatide. There is no comparative evidence about this.	Comment noted. Comment noted. The Committee concluded that while it may be that treatment with denosumab would be started in secondary care, it would be subsequently delivered almost exclusively in primary care. For further details please see FAD section 4.17. Comment noted.

Role*	Section	Comment	Response
NHS professional 2	5	CSAS rapid evidence review estimates that an average sized PCT (approximately 300,000 population) would fund this treatment for about 1600 patients. The annual cost of treatment is estimated at by the manufacturer at £366 per patient per year, equating to an estimated spend of £585,600 per year per PCT as compared with £47,840 for non-proprietary alendronic acid (from BNF prices). It would be helpful to PCTs for there to be more clarity around the statement "unable to take oral bisphosphonate" and where IV bisphosphonates should be placed in any care pathway compared to denosumab in secondary prevention. The economic analysis in secondary prevention does not give a lot of detail of denosumab compared to IV bisphosphonates, nor does it indicate whether denosumab would be prescribed in primary or secondary care. Our local primary care clinicians have advised that they would not be comfortable with prescribing denosumab. There is not the evidence available to support the clinical specialist opinion at 4.14	Comment noted. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources. (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 to 6.2.6.3). Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. Comment noted. Postmenopausal women who are unable to take oral bisphosphonates are those who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. Please see FAD section 1. Comment noted. The Committee concluded that while it may be that treatment with denosumab would be started in secondary care, it would be subsequently delivered almost exclusively in primary care. For further details please see FAD section 4.17.

Role*	Section	Comment	Response
NHS professional 3	1	Adoption of this draft recommendation as it stands would add to the burden on community nursing and GP practice workloads (as it is a sub-cutaneous injection and will be used in older people), and on the primary care prescribing budget, without any evidence of patient orientated outcomes, or disinvestment opportunity. Alendronic acid 70mg once weekly costs about £17 plus community pharmacy dispensing fees per patient per year and has evidence for prevention of symptomatic fractures. Denosumab costs £366 plus administration costs (and possibly community pharmacy dispensing fees too) per patient per year, but has no patient-orientated outcome evidence.	Comment noted. Committee discussed whether administering denosumab would be part of general medical services or whether it would be regarded as an enhanced service for which an additional payment would be negotiated, and it noted the comments received during consultation on the ACD. The clinical specialists stated that because treatment with denosumab would not involve substantial additional activities to standard practice in managing osteoporosis, it is likely that it would be provided as part of general medical services. The Committee accepted the views of the clinical specialists that there were no specific safety concerns around the use of denosumab and that follow-up in secondary care would not be necessary, and hence it was not persuaded to alter its opinion that denosumab is likely to be provided as part of general medical services in primary care. For further details please see FAD section 4.17.

Role*	Section	Comment	Response
NHS professional 3	2	The draft recommendations include the use of denosumab for primary and secondary prevention. Efficacy in trials has been measured solely with surrogate markers (disease-orientated outcomes such as radiographic vertebral fractures) not patient-orientated outcomes such as reduction in symptomatic fracture rate. Only one trial, Brown et al., 2009, used our fist line drug for the treatment of osteoporosis, alendronate, as the comparator. This was a non-inferiority trial, and was not powered sufficiently to compare fracture rates between the treatment groups. Because of this there is no evidence to show that resources will be able to be diverted from orthopaedics to pay for this drug, even at a later date. Therefore funding will need to removed from elsewhere in order for the PCT to afford this. The evidence only extends to 3 years of use. As this is a novel agent, a full monoclonal antibody with the potential for immune system effects, safety data beyond 3 years is needed, as this is likely to be a lifelong medication. Whilst none of the trials saw an increase in the rate of serous infections or neoplasms, an increased rate of eczema and cellulitis was reported in the FREEDOM study.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD. Comment noted.
NHS professional 3	3	Although the draft recommendations place denosumab for use only in patients who are unable to comply with the special instructions for the administration of oral bisphosphonates, are intolerant of oral bisphosphonates or for whom treatment with oral bisphosphonates is contraindicated, it is widely agreed by pharmacists that many patients do not take bisphosphonates in the absolutely correct manner, so the population to which this proposed guidance would apply may be larger than the manufacturer estimated in its calculations.	Comment noted.

Role*	Section	Comment	Response
NHS professional 3	4	Efficacy in trials has been measured using only surrogate markers (disease-orientated outcomes e.g. radiographic vertebral fractures) not patient-orientated outcomes e.g. reduction in symptomatic fracture rate. Only one trial, Brown et al 2009, used our 1st line osteoporosis treatment drug, alendronate, as comparator. This was a non-inferiority trial, and wasnt powered sufficiently to compare fracture rates between treatment groups. Therefore there is no evidence that disinvestment in orthopaedics will be possible to pay for denosumab, even at a later date. Therefore funding will need to removed from elsewhere in order for the PCT to afford this. The evidence only extends to 3 years of use. As this is a novel agent, a full monoclonal antibody with potential for immune system effects, safety data beyond 3 yrs is needed as use is likely to be lifelong. No trial saw an increase in the rate of serous infections or neoplasms, but an increased rate of eczema & cellulitis was reported in the FREEDOM study. Pharmacists widely agree that many patients do not take bisphosphonates in the absolutely correct manner so this proposed guidance may apply to a larger population than estimated.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD. Comment noted.
NHS professional 3	5	The costing statement must take into account all the other options for treatment of postmenopausal women for the primary and secondary prevention of osteoporotic fractures, where patients are not able to take bisphosphonates. Because of the suspected large number of patients who do not take bisphosphonates absolutely correctly, the costing statement should also take into account that some patients who are already prescribed generic alendronate (at about £17 plus up to 13 community pharmacist dispensing fees per patient per year) may be changed onto denosumab (at £366 plus administration costs, and potentially plus up to 2 community pharmacist dispensing fees, per patient per year).	Comment noted.
NHS professional 3	6	The review date should be brought forward to 2 years from publication, by which time more evidence relevant to the safety / risks of the drug will be available from post-marketing surveillance.	Comment noted. The guidance on this technology will be considered for review at the same time that NICE technology appraisal guidance 160 and 161 (2008; amended 2010) are considered for review.

Role*	Section	Comment	Response
NHS professional 4	1	Although I understand the committees intention to keep this guidance in line with that already put forward in TA160/161 (I have previously argued that that is based on unduly conservative assumptions but clearly that is a battle I have already lost) these recommendations do not bear face validity against those proposals. The threshold values proposed here are more restrictive than those proposed in previous guidance for strontium and raloxifene. The clinical evidence cleraly indicates that denosumab has much better fracture reduction efficacy either of these agents. The cost of the two drugs is not dissimilar (£366 for denosumab and £333 for strontium) and so I am concerned that soemthing has gone awry in the modelling which has led to what appears to me to be anomalous advice. In addition I would urge the committee to give more consideration to the plight of that small group of women who are truly bisphosphonate sesnitive, eg those who have developed urticaria on treatment (in my practice rare but not unheard of say 2-3 cases per year in a large tertiary cente). Denosumab is perhaps the really only effective antiresorptive available to them.	Comment noted. The criteria for the use of denosumab is the same as for strontium ranelate for primary prevention, and less restrictive than strontium ranelate for secondary prevention. For considerations of the evidence, please see section 4 of the FAD. Comment noted.
NHS professional 4	3	I agree with the ERG that zoledronate should be the real comparator but this gives us a problem as that has not been appraised by NICE. Surely for consistencys sake the correct comparator is the basket of treaments in TA160/161	The Committee concluded that although treatment with denosumab may be started in secondary care, it will be subsequently delivered almost exclusively in primary care, unlike the administration of zoledronate, use of which will remain in a secondary care setting. The Committee regarded the main comparators for denosumab to be those treatments delivered in primary care when oral bisphosphonates were unsuitable (no treatment, strontium ranelate, raloxifene). Please see FAD sections 4.3 and 4.18.

Role*	Section	Comment	Response
NHS professional 5	1	The PCTs concern is that the number that claim are intolerant to bisphosphonates are high and the financial impact may be a lot higher than predicted. GPs will request an administarion fee if patients cannot self administer.	Comment noted.
NHS professional 5	2	Significant cost implications to PCT if funding primary and secondary prevention £366 per patient per year vs generic bisphosphonate eg alendronic acid approx £13/annum	Comment noted. Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD.
NHS professional 5	4	NNT denosumab Â 333 for hip fracture vs 91 for alendronate raises concern for use. Efficacy in trials has not demonstrated significant reduction in fractures. Risk of immunosuppression has been demonstrated in trials of 36 month duration further consideration needed. There is only a single trial comparing denosumab with alendronate does not compare fracture incidences. Denosumab is cost effective for secondary prevention, as compared with teriparatide, in women eligible for treatment with teriparatide as per NICE guidance. Shown to be effective and cost effective in some subgroups for secondary prevention and this might represent good value for money, however PCT will need to find additional resources and where these resources might be taken.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk $p < 0.001$) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7.

Role*	Section	Comment	Response
NHS professional 5	5	Local health economy approx 850,000 population estimates 4250 patients would be treated equating to an estimated financial impact of £1,555,500 per year as compared with £59,160 for non-proprietary alendronic acid (from BNF prices). This will have a significant impact on finances available to deliver other local priorities.	Comment noted. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources. (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 to 6.2.6.3). Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD.

Role*	Section	Comment	Response
NHS professional 6	4	• Significant cost implications to PCT if funding primary and secondary prevention £366 per patient per year vs generic bisphosphonate eg alendronic acid. • NNT denosumab 333 for hip fracture vs 91 for alendronate raises concern for use. • Efficacy in trials has not demonstrated significant reduction in fractures. • Risk of immunosuppression has been demonstrated in trials of 36 month duration further consideration needed. • There is only a single trial comparing denosumab with alendronate does not compare fracture incidences. • Denosumab is cost effective for secondary prevention, as compared with teriparatide, in women eligible for treatment with teriparatide as per NICE guidance. • Shown to be effective and cost effective in some subgroups for secondary prevention and this might represent good value for money, however PCT will need to find additional resources and where these resources might be taken. • Local health economy approx 850,000 population estimates 4250 patients would be treated equating to an estimated financial impact of £1,555,500 per year as compared with Â£59,160 for non-proprietary alendronic acid (from BNF prices).	Comment noted. Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD. Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk $p < 0.001$) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7.

Role*	Section	Comment	Response
NHS professional 6	5	• Local health economy approx 850,000 population estimates 4250 patients would be treated equating to an estimated financial impact of £1,555,500 per year as compared with Â£59,160 for non-proprietary alendronic acid (from BNF prices). • Significant cost implications to PCT if funding primary and secondary prevention £366 per patient per year vs generic bisphosphonate eg alendronic acid.	Comment noted. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources. (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 to 6.2.6.3). Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD.
Other 1	1	The phrase Â "unable to comply with the special instructions for the administration of oral bisphosphonates" has no READ code and cannot be audited. We find that reasons for stopping oral bisphosphonates are usually given as intolerance. We would like to see this phrase altered to who are unable to comply with etc due to physical inability or difficulty in remaining in an upright position or who have difficulty in swallowing or have a documented oesophageal problem. We also find in practice that patients unable or unwilling to take one bisphosphonate can usually be transferred onto another or to a weekly or monthly formulation. We would like to see the recommendation including a phrase suggesting more than one oral bisphosphonate. We do not recognise the clinical need for another treatment to add to those already available.	Comment noted. Section 1 of the FAD states that denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments.
Other 1	2	2.2. the theoretical risks (malignancies, serious infections) of using a monoclonal antibody long term which concerned the FDA should be mentioned. The trial extensions looking at long term safety (NCT00523341 and NCT00325468) have not reported. It should be mentioned in section 2 that this is the case.	Comment noted. The Committee concluded that the available clinical evidence on the adverse effects associated with denosumab indicated that it was a well tolerated treatment for the prevention of osteoporotic fragility fractures in postmenopausal women. See FAD section 4.9.
Other 1	3	3.1: FREEDOM does not exactly reflect the range of patients expected to be given this drug within the NHS since it is not stated if the subjects were treatment naive. 3.2: the primary endpoint is not patient oriented. Treatment should	Comment noted. Comment noted. The primary outcome in the FREEDOM study of denosumab compared with

Role*	Section	Comment	Response
		aim at reducing clinically apparent fractures. The absolute risk reduction for the secondary end point of hip fracture would appear to be only 0.3%.	placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk p < 0.001) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7.
		3.8 Persistence & compliance varies considerably depending on daily/weekly/monthly regimens. Aggregation could be misleading.	Comment noted
		3.10 Does not reflect clinical experience, as noted by the ERG, patients with any fracture have an increased risks of other fractures in various sites.	Comment noted
		3.18 the assumptions on adverse events & administrations costs are not stated clearly but we would strongly endorse the ERGs view that more than 2 GP visits would be needed. In addition, if given in primary care this would be an enhanced service at higher cost. Also monoclonal antibodies need a level of monitoring for ADRS not apparently reflected in the costs	Comment noted. The Committee discussed whether administering denosumab would be part of general medical services or whether it would be regarded as an enhanced service for which an additional payment would be negotiated, and it noted the comments received during consultation on the ACD. The Committee concluded that while treatment with denosumab may be started in secondary care, it would be subsequently delivered almost exclusively in primary care. For further details please see FAD section 4.17.
		3.28 We strongly endorse the ERGs comments	

Role*	Section	Comment	Response
Other 1	4	4.6 The lack of direct head to head comparisons with current treatments is a considerable disadvantage. Osteoporosis treatment is well established with a variety of alternative treatments. The indirect comparisons are open to misinterpretation and the committee did not emphasise this sufficiently. 4.10 Whilst the committee took some account of the ERGs comments we do not believe that enough weight was given to their concerns and we believe an economic appraisal incorporating their suggestions would make denosumab much less cost effective. 4.14 We believe that primary care will be less likely to take on the prescribing of a monoclonal antibody than the clinical experts believe. We are not aware of any biological therapies being routinely used outside secondary care even with a shared care protocol. We believe that a homecare company might be more likely - at additional costs.	The Committee noted that, because the FREEDOM study did not provide a head-to-head comparison of denosumab against all relevant comparators, the manufacturer carried out a random-effects meta-analysis to obtain direct estimates for each treatment compared with placebo. The Committee noted the lack of a direct comparison of denosumab with active comparators. It was, therefore, unable to make a conclusion about the relative clinical effectiveness of denosumab, but was satisfied with the evidence on the direct estimates for each treatment compared with placebo and concluded that the methods used in the meta-analysis were sufficiently robust for use in the economic analysis. Despite weaknesses in the evidence base, decisions still have to me made about the use of technologies. See section 5.1.6 of the 'Guide to the methods of technology appraisal', June 2008. Comment noted. The Committee noted the ERG's view that administration of denosumab may not be provided in primary care. However, the clinical specialists stated that there is no reason why denosumab should only be used in secondary care. The clinical specialists highlighted that because denosumab is a new biological agent they expected that, initially, treatment would be started in secondary care, but with follow-up almost exclusively in primary care (except for women with severe osteoporosis, who may be followed up in secondary care in line with current UK clinical practice). For further details please see FAD section 4.17.

Role*	Section	Comment	Response
NHS professional 7	2	1.The treatment has the risk of immunosuppression. Safety has been demonstrated in trials of 36 month duration, but would need further consideration. 2.The issue of using a powerful monoclonal antibody in asymptomatic patients really needs to be properly considered within a long term time horizon. FDA states that the occurrence of serious infection, development of new malignancies, potential for tumour progression in patients with cancer, possible suppression of bone remodelling and dermatologic adverse events may raise questions about the risk/benefit balance for the osteoporosis prevention indication the FDA has not approved Denosumab for prevention of osteoporosis in postmenopausal women with early bone loss 3.Long-term safety data is not yet available and the FDA highlights the slightly increased incidence of serious infection with denosumab, potential increased risk of malignancy and dermatologic side effects as issues for consideration. 4.Evidence Review Group should use published literature and expert advice to explore, characterise and quantify long term risks of monoclonal antibody use and set this into the context of the clinical risk / ben balance in sec prev	Comment noted. Comment noted. Comment noted. The clinical specialists confirmed that 14,000 women have received denosumab and that it was well tolerated. The Committee concluded that the available clinical evidence on the adverse effects associated with denosumab indicated that it was a well tolerated treatment for the prevention of osteoporotic fragility fractures in postmenopausal women. Please see FAD section 4.9.

Role*	Section	Comment	Response
NHS professional 7	3	1.There is only a single trial comparing denosumab with alendronate and denosumab is better at improving bone mineral density, but fracture incidences were not compared. It is cost effective (slightly less effective but much less costly) for secondary prevention, for women eligible for treatment with teriparatide as per NICE guidance. 2.There are several treatment options for women with osteoporosis including weight bearing exercise, dietary calcium and vitamin D, bisphosphonates, raloxifene and strontium ranelate. The appraisal should consider a range of clinically appropriate comparators.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee concluded that denosumab was a cost effective use of resources and may be an option for secondary prevention of osteoporotic fragility fractures in women for whom oral bisphosphonates are unsuitable. Please see FAD section 4.26. Comment noted.

Role*	Section	Comment	Response
NHS professional 7	4	4. The fact that this is a drug that is injectable by a practice nurse (rather than having to pay day case hospital admission) will need to be built into the economic model, the affordability and any implementation guidance. One issue to pick up that should be picked up in the TA, but MUST be picked up in implementation guidance, is that any cost savings (from shifting activity from secondary care ? day cases ? can ONLY be realised in cash by NHS commissioners, if reductions in secondary care acivity are seen (ie available / freed up capacity will soon be filled by something else). This is a critical issue in the economic appraisal of cost effectivness ? it relates to the cost effectivness of a specific technology in the pathway of care as a whole (and the cost to the NHS as a whole), rather than an isolated view of a technology out of context of the whole pathway. 5. Some of the existing treatments are available generically and at low cost. The cost of denosumab is not yet available and this will have a bearing on the cost-effectiveness of therapy compared to alternative	Comment noted. . Comment noted. Denosumab is only recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD. The price of denosumab is now publically available. Please see FAD section 2.4.

Role*	Section	Comment	Response
NHS professional 7	5	1.The published draft recommendations envisage the use of denosumab for primary as well as secondary prevention. This would have implications for commissioners of postmenopausal osteoporosis services as denosumab, costing Â£366 per patient per year, would be used instead of a generic bisphosphonate eg alendronic acid 2.The drug is currently recommended for specific clinical subgroups, but commissioners need to consider how they would monitor use in subgroups and prevent broader use. 3.Pricing for this new drug is not yet known. there are no head to head comparator trials for antifracture efficacy. The cost of denosumab is not yet known, but will be critical if clinical differences are marginal with its competitors ? as indeed the initial data seems to be showing.	Comment noted. Denosumab has only been appraised and recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD. Comment noted. Comment noted. The Committee noted that, because the FREEDOM study did not provide a head-to-head comparison of denosumab against all relevant comparators, the manufacturer carried out a random-effects meta-analysis to obtain direct estimates for each treatment compared with placebo. The Committee noted the lack of a direct comparison of denosumab with active comparators. It was, therefore, unable to make a conclusion about the relative clinical effectiveness of denosumab, but was satisfied with the evidence on the direct estimates for each treatment compared with placebo and concluded that the methods used in the meta-analysis were sufficiently robust for use in the economic analysis. Despite weaknesses in the evidence base, decisions still have to me made about the use of technologies. See section 5.1.6 of the 'Guide to the methods of technology appraisal', June 2008. The price of denosumab is now publically available. Please see FAD section 2.4.

Role*	Section	Comment	Response
NHS professional 8	1	Although positioned in the treatment pathway after the bisphosphonates, it is likely that there will be an extension of use outside of the NICE recommendations. As osteoporosis is a common condition, and the bisphosphonates are available generically at low cost. the cost impact of the guidance to PCTs will be high (up to ten times the costs).	Comment noted.
NHS professional 8	3	There are already several effective treatment options available to treat osteoporosis including weight bearing exercise, dietary calcium and vitamin D, bisphosphonates, raloxifene and strontium ranelate. There is only one phase III active comparator trial of denosumab versus alendronate for the treatment of postmenopausal osteoporosis. While denosumab led to greater BMD improvements at all sites compared with alendronate, the trial was not powered to detect a difference in fracture rate.	Comment noted. Denosumab has only been appraised and recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD.

Role*	Section	Comment	Response
NHS professional 8	4	Safety - This is the first drug of its class to be used in the treatment of osteoporosis. It is likely to be used in a large number of patients in the treatment of a long term condition and the safety profile beyond 36 months has yet to be established. Cost-effectiveness - The NICE appraisal committee has accepted the case that denosumab will be administered predominantly in in primary care. Given the lack of long term safety data (as outlined above), this may be a flawed assumption and we believe that our GPs are unlikely to prescribe this treatment. We would therefore concur with the ERG cost per QALY estimates of assuming secondary care administration.	Comment noted. Comment noted. The Committee noted the ERG's view that administration of denosumab may not be provided in primary care. The clinical specialists highlighted that because denosumab is a new biological agent they expected that, initially, treatment would be started in secondary care, but with follow-up almost exclusively in primary care (except for women with severe osteoporosis, who may be followed up in secondary care in line with current UK clinical practice). The Committee accepted the views of the clinical specialists that there were no specific safety concerns around the use of denosumab and that follow-up in secondary care would not be necessary. Therefore, it was not persuaded to alter its opinion that denosumab is likely to be provided as part of general medical services in primary care. Please see FAD section 4.17.
NHS professional 9	1	Denosumab is a monoclonal antibody and treatment has the risk of immunosuppression. Safety has been demonstrated in trials of 36 month duration, but would need further consideration for longer term treatment	Comment noted.

Role*	Section	Comment	Response
NHS professional 9	3	Efficacy in trials has been measured with surrogate markers (bone mineral density), with no demonstrated significant reduction in fractures. There is only a single trial comparing denosumab with alendronate and denosumab is better at improving bone mineral density, but fracture incidences were not compared. Denosumab is cost effective (slightly less effective but much less costly) for secondary prevention, as compared with teriparatide, in women eligible for treatment with teriparatide as per NICE guidance.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk $p < 0.001$) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7.
NHS professional 9	4	Denosumab has been shown to be effective and cost effective in some subgroups for secondary prevention and this might represent good value for money, however PCTs need to consider whether additional resources would be required to fund secondary prevention, and from where these resources might be taken. An average sized PCT (approximately 300,000 population) would potentially fund this treatment for about 1600 patients. The annual cost of treatment is estimated by the manufacturer at £366 per patient per year, equating to an estimated financial impact of £585,600 per year per PCT as compared with £47,840 for non-proprietary alendronic acid (from BNF prices). The drug is currently recommended for specific clinical subgroups, but commissioners need to consider how they would monitor use in subgroups and prevent broader use.	Comment noted.

Role*	Section	Comment	Response
NHS professional 9	5	Denosumab is a monoclonal antibody and treatment has the risk of immunosuppression. Safety has been demonstrated in trials of 36 month duration, but would need further consideration for longer term treatment	Comment noted.
NHS professional 10	1	long term safety data is not available for this treatment which as a full monoclonal antibody could potentially affect immune system. FDA has stated that occurence of serious infection, malignancy, tumour progression, possible suppression of bone remodelling and dermatological adverse events may raise questions about risk benefit balance for the osteoporosis prevention indication - this is particularly relevant in primary fracture prevention where bisphosphonates infusion is available where patients are unable to comply with the special administration requirements of oral bisphosponates and which should be considered before a biological with as yet an unproven long term safety record. May have a role in use in secondary prevention where patients have fractured despite bisphosphonate use.	Comment noted. The clinical specialists confirmed that 14,000 women have received denosumab and that it was well tolerated. The Committee concluded that the available clinical evidence on the adverse effects associated with denosumab indicated that it was a well tolerated treatment for the prevention of osteoporotic fragility fractures in postmenopausal women. Please see FAD section 4.9
NHS professional 10	2	Full human monoclonal antibody - no long term safety data, longest trial was 36 months. Potential for serious adverse reactions (see comment above) compared to existing treatments, this needs to be established before such widespread use is approved.	Comment noted. The clinical specialists confirmed that 14,000 women have received denosumab and that it was well tolerated. The Committee concluded that the available clinical evidence on the adverse effects associated with denosumab indicated that it was a well tolerated treatment for the prevention of osteoporotic fragility fractures in postmenopausal women. Please see FAD section 4.9
NHS professional 10	3	Support use of denosumab 2nd line to zolendronate infusion (where oral alendronate or other generic bisphosphonate is inappropriate/ not tolerated or poor compliance) Denosumab has been shown to be effective and cost effective in some subgroups for secondary prevention and this might represent good value for money. However in primary prevention (i.e. no previous fracture) denosumab does not seem to demonstrate cost effectiveness compared to zolendronate infusion.	Comment noted. As this is a single technology appraisal (STA), NICE can only issue guidance on the use of denosumab in the NHS. Comment noted. The Committee had already concluded that although treatment with denosumab may be started in secondary care, it will be subsequently delivered almost exclusively in primary care, unlike the administration of zoledronate, use of which will remain in secondary care. As the Committee regarded the main

Role*	Section	Comment	Response
			comparators for denosumab to be those treatments delivered in primary care when oral bisphosphonates were unsuitable (no treatment, strontium ranelate, raloxifene), it did not regard these issues to be central to the decision problem. See FAD section 4.18.
		Denosumab has been shown to be effective in improving bone mineral density compared with placebo and in the single trial comparing denosumab and alendronate, denosumab was more effective in improving bone mineral density. But efficacy in trials has been measured with surrogate markers (bone mineral density), with no demonstrated significant reduction in fractures compared to alendronate.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk $p < 0.001$) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7.
		Most likely to be initiated and administered under secondary care until more is known about long term safety. Biologicals are relatively new and the majority of GPs have little experience with this class of drugs and are likely to be cautious about accepting responisbility for administration and monitoring yet.	Comment noted. The Committee noted the ERG's view that administration of denosumab may not be provided in primary care. The clinical specialists highlighted that because denosumab is a new biological agent they expected that, initially, treatment would be started in secondary care, but with follow-up almost exclusively in primary care (except for women with severe osteoporosis, who may be followed up in secondary care in line with

Role*	Section	Comment	Response
			current UK clinical practice). The Committee accepted the views of the clinical specialists that there were no specific safety concerns around the use of denosumab and that follow-up in secondary care would not be necessary. Therefore, it was not persuaded to alter its opinion that denosumab is likely to be provided as part of general medical services in primary care. Please see FAD section 4.17.
NHS professional 10	4	This needs more clarity as to place in therapy of all second line options after oral bisposponates. Consider as an optioncan be very widely interpreted and will need a lot of localising and agreeing more robust pathways and appropriate targetting.	Comment noted.
NHS professional 10	5	This has significant potential cost implications in primary care, particularly if the decision is made to recommend for primary as well as secondary prevention of fractures. With over £500K additional costs per average PCT (300,000 population) - based on CSAS rapid review. careful managemnt will be needed to ensure that it is targeted appropriately. This guideline as it stands is very broad and does not clearly designate its place in therapy compared to other second line choices zolendronate, strontium, teriparatide, and is open to significant interpretion.	Comment noted.

Role*	Section	Comment	Response
NHS professional 11	1	Recommendations based on one placebo-controlled study measuring BMD -where is patient outcome evidence? No evidence that denosumab is better than standard therapy, i.e. bisphosphonates such as alendronate Would recommend that denosumab is not accredited for primary / secondary prevention until it has clear evidence showing benefit (fractures) compared to exisiting treatment	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk $p < 0.001$) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7. Denosumab has only been appraised and recommended for postmenopausal women who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have, an intolerance of or a contraindication to those treatments. See section 1 of the FAD.
NHS professional 11	2	Monoclonal antibodies have significant adverse effects and what is long term effects? also adminsitration is via s/c injection - this will add to pressures on acute / community staff	Comment noted.
NHS professional 11	3	s/c administration will not be possible for many patients due to primarily age-related problems, e.g. eyesight, dexterity etc - therefore is this a relatively easy formulation? NO	Comment noted.

Role*	Section	Comment	Response
NHS professional 11	5	Could create massive cost pressures for PCTs /commissioners and this is based on flimsy evidence at best since no patient-related outcomes have been published. Not a good use of NHS resources	Comment noted.
NHS professional 12	1	Concerns that the criteria of unable to comply with special instructions is too vague - for example, it could be applied to patients in care homes and lead to immense cost pressures when considered with current alternatives, including additional costs of administration for those who cannot self-administer, organising additional resource to undertake this. HRT regimes were not reported as being difficult to adhere to, yet too had an adminstration schedule. It also fails to mention how this technology fits in with other drugs available for treatment and prevention of osteoporosis. How will women at increased risk of fracture be defined?	Comment noted. Please see section 1 of the FAD.
NHS professional 12	2	Lack of long-term safety data (e.g. immunosuppression) & ADRs such as infections especially as the proposed use with the vague criteria may potentially mean many women could qualify for the treatment. Current biologics are all PbR excluded, therefore there is no incentive for a provider to negotiate discounts, and if they do, to pass this onto the PCTs.	Comment noted.

Role*	Section	Comment	Response
NHS professional 12	3	Only one direct comparator trial with current practice, and this did not compare incidences of fractures instead looked at surrogate marker of BMD. Studies mainly looked at vertebral fractures, when it is hip fractures that cause the increased morbidity and mortality, so costs off set by the technology are not transparent.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk $p < 0.001$) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7.
NHS professional 12	4	Main data from placebo trial only rather than current comparators.	Comment noted. The Committee noted that, because the FREEDOM study did not provide a head-to-head comparison of denosumab against all relevant comparators, the manufacturer carried out a random-effects meta-analysis to obtain direct estimates for each treatment compared with placebo. The Committee noted the lack of a direct comparison of denosumab with active comparators. It was, therefore, unable to make a conclusion about the relative clinical effectiveness of denosumab, but was satisfied with the evidence on the direct estimates for each treatment compared with placebo and concluded that the methods used in the meta-analysis were sufficiently robust for use in the economic analysis.

Role*	Section	Comment	Response
NHS professional 12	5	Vague criteria of unable to comply with.... may mean that more women will use this technology than estimated or as modelled by the manufacturer, leading to diversion of funds from other utilities.	Comment noted.
NHS professional 12	6	The demand for this in accordance with licensed indication will be large, so June 2013 likely to be too late for PCTs.	Comment noted.
Pharmaceutical industry	4	The efficacy is measured using surrogate markers with no demonstration of reduction in fractures. There is still considerable debate on the strength of the link between bone density and actual fracture risk. We would support the use of denosumab for secondary prevention as an alternative to teriparatide.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk $p < 0.001$) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7.

Role*	Section	Comment	Response
Pharmaceutical industry	5	The financial implication of this would be significant and restrict investment in other areas. We have an active osteoporosis service in this area and bearing in mind the high numbers of patients unable to tolerate/comply with bisphosphonates We do not use the risk factors described above in isolation - we use the frax tool and therefore clinicians will need to show a separate assessment in order to use the drug. We will also have to develop commissioning policies for the use of the drug in other clincial groups such as men and pre-menopausal women There may be DEXA capacity and cost implications re additional scans to determine if bone density has dropped to a level for patients to be strated on denosumab	Comment noted. The Committee was not persuaded that recommendations about treatment should be based on absolute risk as calculated using FRAX and that the stepped approach of assessing fracture risk is required to ensure the effective allocation of NHS resources. The Committee concluded that using a combination of T score, age and a number of independent clinical risk factors for fracture remained more appropriate for defining treatment recommendations in this appraisal. Please see FAD section 4.15 of the FAD.
NHS professional 13	1	The recommendation for use as primary prevention is unreasonable in view of the limited fracture data, lack of long-term safety data, high cost compared with generic bisphosphonates, and lack of comparison with other treatment options. In the pivotal trial, the number needed to treat for clinical vertebral fractures was around 56 for 3 years, and around 200 for 3 years for hip fracture despite 24% of the trial population already having had a fracture and so being at higher risk than a primary prevention cohort. Use of denosumab for primary prevention should not be a priority for NHS funding.	Comment noted.

Role*	Section	Comment	Response
NHS professional 14	1	The published draft recommendations envisage the use of denosumab for primary as well as secondary prevention. This would have implications for commissioners of postmenopausal osteoporosis services as denosumab, costing £366 per patient per year, would be used instead of a generic bisphosphonate eg alendronic acid. An average PCT (approximately 300,000 population) would fund this treatment for about 1600 patients. The annual cost of treatment is estimated at by the manufacturer at £366 per patient per year, equating to an estimated spend of £585,600 per year per PCT as compared with £47,840 for non-proprietary alendronic acid (from BNF prices). In my PCT estimated 1900 patients at a cost of £695,400. Very difficult to define intolerance to oral bisphosphonates, and failure to comply with the special instructions for administration would allow broadening of use-need to have more precise criteria for use.	Comment noted. The Committee does not consider the affordability, that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources. (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 to 6.2.6.3).
NHS professional 14	2	The treatment has the risk of immunosuppression. Safety has been demonstrated in trials of 36 month duration, but would need further consideration.	Comment noted.
NHS professional 14	3	We have not authorised the use of zolendronic acid within the PCT as was not considered to be cost-effective in osteoporosis. Recognise that poor compliance is an issue with oral bisphosphonates, but probably better value to fund a reminder and support service for patients.	Comment noted.

Role*	Section	Comment	Response
NHS professional 14	4	Efficacy in trials has been measured with surrogate markers (bone mineral density), with no demonstrated significant reduction in fractures. There is only a single trial comparing denosumab with alendronate and denosumab is better at improving bone mineral density, but fracture incidences were not compared. It is cost effective (slightly less effective but much less costly) for secondary prevention, for women eligible for treatment with teriparatide as per NICE guidance. Denosumab has been shown to be effective and cost effective in some subgroups for secondary prevention and this might represent good value for money, however additional resources will be required not only for the cost of the drug but also for auditing and closely monitoring the usage to avoid broader use.	Comment noted. The primary outcome in the FREEDOM study of denosumab compared with placebo was incidence of new radiographically diagnosed vertebral fractures. Secondary outcomes were time to first non-vertebral fracture and time to first hip fracture. Please see FAD section 3.2. The Committee noted that the FREEDOM trial showed that there was a statistically significant 68% reduction in the relative risk $p < 0.001$) for the 36 month incidence of new radiographically diagnosed vertebral fractures. The Committee also noted that denosumab significantly reduced the risk of non-vertebral fracture (HR 0.80; 95% CI 0.67 to 0.95; relative reduction of 20%) and of hip fracture (HR 0.60, 95% CI 0.37 to 0.97; relative reduction of 40%). The Committee concluded that the evidence from the FREEDOM trial demonstrated that denosumab was effective in reducing the risk of fracture in postmenopausal women compared with placebo. See FAD section 4.7.
NHS professional 15	1	[1] Primary Prevention: This still leaves ALOT of post-menopausal women with a proven disease [osteoporosis]who cannot tolerate any of the bisphosphonates without any treatment until they inevitably fracture : ie hugh gaping hole of 2nd line treatments : quite unlike statins when you start with cheap simva and then work along. Denosumab is about the same price as Atorvastatin and you dont tell men with IHD sorry, you need to have a heart attack before I can prescribe another statin. The GP community find this unethical. [2] DXAs: GPs are unable to access DXAs for women 75 yrs due to NICE TAG 161: so by saying you have to have a DXA in women 75 you will actually cost the NHS a great deal more in 2ndry referrals: have you costed this?	Comment noted. Comment noted.