NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Denosumab for the Prevention of Osteoporotic Fractures in Postmenopausal Women

Manufacturer Response to Appraisal Consultation Document

Amgen UK Ltd.

Submitted 9 July 2010

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) for denosumab (June 2010). Amgen is pleased that the NICE preliminary recommendation has recognised the value of denosumab in the prevention of osteoporotic fractures in postmenopausal women and recommends its use in both primary and secondary prevention of fragility fractures.

Our comments on specific aspects of the ACD are included below, and we also address some factual inaccuracies and aspects which may benefit from improved wording to avoid misinterpretation.

Our comments below refer to the ACD and the Evidence Review Group (ERG)report. Where they refer to the ERG report, this has been indicated.

Section A – Decision problem

1. Has all of the relevant evidence been taken into account?

All of the relevant evidence has been taken into account.

Section B – Clinical and cost-effectiveness

2. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

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.

- 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

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.

Comments Regarding Current ACD Text

Section	Current Text	Comments	Proposed Text/Action
2.2	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). <u>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)</u>.
2.2	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 <u>adverse events</u> and contraindications, see the summary of product characteristics.

Section	Current Text	Comments	Proposed Text/Action
3.4	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.

Section	Current Text	Comments	Proposed Text/Action
3.5	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.

Section	Current Text	Comments	Proposed Text/Action
3.5 (and Section 4.2.1 of ERG report, p32)	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.
3.6	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.

Section	Current Text	Comments	Proposed Text/Action
3.7	…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
3.8	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.

Section	Current Text	Comments	Proposed Text/Action
3.9	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.

Section	Current Text	Comments	Proposed Text/Action
3.15 (and Section 3.31 in ERG report, p22	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
3.23	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.

Section	Current Text	Comments	Proposed Text/Action
3.28	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).	Proposed text: The ERG identified several <u>aspects of the manufacturer's economic analysis which in their opinion required additional investigation</u>, 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.

Section	Current Text	Comments	Proposed Text/Action
3.28 contd.		• 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.	
3.31	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 <u>would favour less efficacious therapies; however, the extent of the effect</u> on the cost-effectiveness estimates <u>remains</u> unclear.
3.32 (and Section 3.31 in ERG report, p22	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 <u>and for denosumab</u>.

Section	Current Text	Comments	Proposed Text/Action
3.34	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.
3.37 (and Section 2.2 of ERG report, p15)	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.

Section	Current Text	Comments	Proposed Text/Action
4.3	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 <u>oral</u> bisphosphonates, or has a contraindication to or is intolerant of <u>oral</u> bisphosphonates)
4.4	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 <u>oral</u> bisphosphonates in the UK
4.4	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 <u>the</u> manufacturer did provide an analysis of denosumab compared with oral bisphosphonates for completeness.

Section	Current Text	Comments	Proposed Text/Action
4.9	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 <u>in osteoporosis</u> have shown that treatment may be <u>rarely</u> associated with osteonecrosis of the jaw.
4.10	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. <u>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</u>.

Section	Current Text	Comments	Proposed Text/Action
4.13	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.
4.16	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.

Section	Current Text	Comments	Proposed Text/Action
4.17	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.
4.17	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.

Section	Current Text	Comments	Proposed Text/Action
4.18	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.

Section	Current Text	Comments	Proposed Text/Action
4.18	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.

Summary of Appraisal Committee's Key Conclusions

Section	Current text	Comments	Proposed text / Action
What is the position of the treatment in the pathway of care for the condition?	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.	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.

Section	Current text	Comments	Proposed text / Action
Adverse effects	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.	The correct terminology should be adverse events rather than adverse effects	Proposed text: The Committee concluded that the available clinical evidence on the adverse <u>events</u> associated with denosumab indicated that it was a well-tolerated treatment for the prevention of osteoporotic fragility fractures in postmenopausal women.
Are there specific groups of people for whom the technology is particularly cost-effective?	…as indicated in the following table'.	The table has been omitted	Proposed action: Please include the missing table.
Most likely cost-effectiveness estimate (given as an ICER)	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.	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: <u>Denosumab had an ICER of £2,046 versus raloxifene</u> 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.

Section C – Implementation

3. 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.

4. 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.