Bone metastases from solid tumours - denosumab: appraisal consultation document

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The Department of Health asked the National Institute for Health and Clinical Excellence (NICE) to produce guidance on using denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours in the NHS in England and Wales. The Appraisal Committee has considered the evidence submitted and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see appendix B) and the public. This document should be read along with the evidence base (the evaluation report), which is available from www.nice.org.uk

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE’s guidance on using denosumab in the NHS in England and Wales.

For further details, see the ‘Guide to the technology appraisal process’ (available at www.nice.org.uk).

The key dates for this appraisal are:

Closing date for comments: 02/07/2012
Third Appraisal Committee meeting: 11/07/2012
Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

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1 Appraisal Committee’s preliminary recommendations

1.1 Denosumab is recommended as an option for preventing skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer, if the manufacturer provides denosumab with the discount agreed in the patient access scheme.

1.2 Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.

1.3 Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from solid tumours other than breast and prostate if:

- zoledronic acid or disodium pamidronate would otherwise be prescribed for these patients and
- the manufacturer provides denosumab with the discount agreed in the patient access scheme.

1.4 Adults with bone metastases from solid tumours currently receiving denosumab for the prevention of skeletal-related events that
4.1 Clinical effectiveness

4.1.1 The Assessment Group identified eight studies (including three of denosumab) – four in patients with breast cancer, two in patients with prostate cancer and two in patients with other solid tumours. The two studies in other solid tumours both included patients with non-small cell lung cancer enabling a separate subgroup analysis of non-small cell lung cancer. The Assessment Group undertook a network meta-analysis to compare denosumab with bisphosphonates and with best supportive care.

Breast cancer

4.1.2 One double-blind randomised controlled trial compared denosumab with zoledronic acid and enrolled patients (n = 2045) with confirmed breast cancer and at least one bone metastasis. Duration of follow-up was event rate driven and was approximately...
In the trial comparing denosumab with zoledronic acid, the incidence of serious adverse events and adverse events leading to analgesic use. The difference was not statistically significant (HR 0.89, 95% CI 0.77 to 1.04, p = 0.1416). There were no differences in EQ-5D scores or first on-study skeletal-related event (HR 0.82, 95% CI 0.71 to 0.95) and the risk of first and subsequent skeletal-related event improved with denosumab compared with zoledronic acid in time to first on-study skeletal-related event (HR 0.82, 95% CI 0.71 to 0.95) and the risk of first and subsequent skeletal-related event (HR 0.77, 95% CI 0.66 to 0.89), though the difference in skeletal morbidity rate was not statistically significant. Denosumab was associated with a statistically significant improvement compared with placebo in time to first on-study skeletal-related event (HR 0.56, 95% CI 0.40 to 0.77), risk of first and subsequent skeletal-related event (HR 0.45, 95% CI 0.28 to 0.72), and skeletal morbidity rate (HR 0.47, 95% CI 0.25 to 0.67). Denosumab was also associated with a statistically significant improvement compared with disodium pamidronate in the trial comparing denosumab with zoledronic acid and disodium pamidronate (RR 0.80, 95% CI 0.66 to 0.97). The study comparing zoledronic acid and disodium pamidronate demonstrated a statistically significant effect favouring zoledronic acid (RR 0.59, 95% CI 0.38 to 0.91).

In the trial comparing denosumab with zoledronic acid, patients in the denosumab group on average had fewer skeletal-related events (0.45 events per patient per year) than patients in the zoledronic acid group (0.58 events per patient per year; p = 0.004). In the other trials included in the network meta-analysis zoledronic acid was associated with fewer skeletal-related events than placebo (0.63 compared with 1.1; p = 0.016). Likewise disodium pamidronate was associated with fewer skeletal-related events than placebo (2.4 compared with 3.7; p < 0.001).

In the trial comparing denosumab with zoledronic acid, the median time to first skeletal-related-related event was not reached in the denosumab group and was 26.4 months in the zoledronic acid group (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.71 to 0.95, p = 0.01 superiority). Skeletal-related events is a composite outcome which in this trial comprised radiation therapy to alleviate pain or prevent fracture, surgery to bone to treat or prevent fractures, and pathologic fracture or spinal cord compression that can result in paraesthesias, incontinence, and paralysis. The study comparing zoledronic acid with placebo reported that median time to first skeletal-related-related event was not reached in the zoledronic acid group compared with 384 days in the placebo group (p = 0.007). Denosumab was associated with a statistically significantly longer median time to first skeletal-related-related event than placebo (12.7 months compared with 7.0 months; p < 0.001). The study comparing zoledronic acid with placebo reported a statistically significant difference favouring zoledronic acid for time to first skeletal-related-related event in patients receiving hormone therapy (415 days for zoledronic acid and 370 days for disodium pamidronate; p = 0.047), but not for patients receiving chemotherapy (349 days for zoledronic acid and 366 days for disodium pamidronate; p = 0.826).

In the trial comparing denosumab with zoledronic acid, the risk of first and subsequent skeletal-related-related event was reduced in the denosumab group compared with zoledronic acid (relative risk [RR] 0.77, 95% CI 0.66 to 0.89, p = 0.001 superiority). This risk was also reduced with denosumab in the subgroups of patients with or without a history of prior skeletal-related-related events. The study comparing zoledronic acid with placebo showed a statistically significant effect favouring zoledronic acid (RR 0.59, 95% CI 0.38 to 0.91). However the difference in skeletal morbidity rate was not statistically significant. Compared with zoledronic acid, denosumab also improved time to first on-study skeletal-related-related event (HR 0.82, 95% CI 0.71 to 0.95) and the risk of first and subsequent skeletal-related-related event (HR 0.77, 95% CI 0.66 to 0.89), though the difference in skeletal morbidity rate was not statistically significant. There were more hypocalcaemia adverse events in the denosumab group than the zoledronic acid group (13% and 6%, respectively). There was a lower rate of adverse events potentially associated with renal impairment in the denosumab group than in the zoledronic acid group (4.9% compared with 8.5% respectively). Acute-phase reactions occurring in the first 3 days after treatment were higher in the zoledronic acid group than in the denosumab group (27.3% compared with 10.4%).

In the same trial, the median time to developing moderate or severe pain in patients with no or mild pain at baseline was statistically significantly longer in the denosumab group than the zoledronic acid group (295 compared with 176 days; HR 0.78, 95% CI 0.67 to 0.92, p = 0.0024). There were no differences in EQ-5D scores or analgesic use.

In the trial comparing denosumab with zoledronic acid, the incidence of serious adverse events and adverse events leading to discontinuation were similar in the denosumab and zoledronic acid groups. There was a higher incidence of hypocalcaemia events (5.5% compared with 3.4%) and lower incidence of hypercalcaemia (1.7% compared with 3.5%) in the denosumab group than in the zoledronic acid group. The rate of osteonecrosis of the jaw was similar between the denosumab group and the zoledronic acid group (2.0% and 1.4% respectively). There was a lower rate of adverse events potentially associated with renal impairment in the denosumab group than in the zoledronic acid group (4.9% compared with 8.5% respectively). In the trial comparing denosumab with zoledronic acid, the incidence of serious adverse events and adverse events leading to discontinuation were similar in the denosumab and zoledronic acid groups (63% compared with 60% and 17% compared with 15% respectively). There were more hypocalcaemia adverse events in the denosumab group than the zoledronic acid group (13% and 6%, respectively). There was a lower rate of adverse events potentially associated with renal impairment in the denosumab group than in the zoledronic acid group (4.9% compared with 8.5% respectively). Acute-phase reactions occurring in the first 3 days after treatment were higher in the zoledronic acid group than in the denosumab group (27.3% compared with 10.4%).

Prostate cancer

One double-blind, randomised, controlled trial compared denosumab with zoledronic acid and enrolled men aged 18 years or older with confirmed prostate cancer and at least one bone metastasis (n = 1901). Follow-up was 41 months. One further randomised controlled trial was included in the network meta-analysis which compared zoledronic acid with placebo (n = 643).

In the trial comparing denosumab with zoledronic acid, median time to first on-study skeletal-related-related event was statistically significantly longer with denosumab than zoledronic acid (20.7 compared with 17.1 months, HR 0.82, 95% CI 0.71 to 0.95, p = 0.008 superiority). In the study comparing zoledronic acid with placebo, zoledronic acid increased the time to first on-study skeletal-related-related event (488 days compared with 321 days; p = 0.009).

In the trial comparing denosumab with zoledronic acid, the risk of developing first and subsequent on-study skeletal-related-related events was reduced by denosumab compared with zoledronic acid (RR 0.82, 95% CI 0.71 to 0.94, p = 0.008). In the trial of zoledronic acid against placebo, zoledronic acid was shown to reduce the risk of first and subsequent skeletal-related-related events compared with placebo (RR 0.64, 95% CI: not reported; p = 0.002).

In the trial comparing denosumab with zoledronic acid, skeletal morbidity rate was statistically significantly lower among patients treated with denosumab than patients treated with zoledronic acid (figures provided academic in confidence). In the study comparing zoledronic acid with placebo, zoledronic acid reduced the skeletal morbidity rate from 1.49 in the placebo group to 0.80 in the zoledronic acid group (p = 0.006).

The results of the network meta-analysis showed that denosumab was associated with a statistically significant improvement compared with placebo in time to first on-study skeletal-related-related event (HR 0.56, 95% CI 0.40 to 0.77), risk of first and subsequent skeletal-related-related event (RR 0.53, 95% CI 0.39 to 0.72) and skeletal morbidity rate (RR 0.52, 95% CI 0.07 to 0.82). Results of the network meta-analysis also showed a statistically significant improvement with denosumab compared with zoledronic acid in time to first on-study skeletal-related-related event (HR 0.82, 95% CI 0.71 to 0.95) and the risk of first and subsequent skeletal-related-related event (RR 0.82, 95% CI 0.71 to 0.94). The result for skeletal morbidity rate was not statistically significant.
4.2 Cost effectiveness

4.2.1 The manufacturer identified 21 published studies that contained economic analyses of bisphosphonates. Twelve papers contained economic evaluations that included incremental cost-effectiveness analysis, of which seven were cost-utility analyses. Of the 12 papers, eight were in breast cancer, two in prostate cancer, one in lung cancer and one in renal carcinoma. The Assessment Group identified 11 studies, one of which included denosumab as an intervention. This study was in patients with prostate cancer and compared denosumab with zoledronic acid. The study used US cost data and reported costs per skeletal-related event avoided.

4.2.2 Of the 11 studies identified by the Assessment Group, seven were in breast cancer, three in prostate cancer and one in lung cancer. Three of the breast cancer studies compared denosumab with zoledronic acid and reported incremental cost-effectiveness ratios (ICERs) for zoledronic acid and denosumab with different cost and outcome measures. The third paper reported that oral ibandronate was cost saving compared with zoledronic acid and reported ICERs for zoledronic acid of between £2124 and £31,476 per QALY gained depending on the country of the cost data. The second reported that denosumab was associated with £11,137 in additional costs per skeletal-related event avoided and £105,976 per QALY gained. The third compared denosumab and zoledronic acid and reported a cost per skeletal-related event avoided for denosumab of £31,532 using a 3-year time horizon. The lung cancer study reported that using UK cost data zoledronic acid was not associated with a statistically significant difference in cost per QALY gained compared with placebo. The lung cancer study also reported ICERs for zoledronic acid of between £2124 and £31,476 per QALY gained depending on the country of the cost data. The third compared denosumab and zoledronic acid and reported a cost per skeletal-related event avoided for denosumab of £31,532 using a 3-year time horizon. The lung cancer study reported that using UK cost data zoledronic acid was not associated with a statistically significant difference in cost per QALY gained compared with placebo.
The manufacturer of denosumab submitted a Markov economic model that assessed the cost effectiveness of denosumab in three patient groups: breast cancer, prostate cancer and other solid tumours (excluding breast and prostate). The model had five health states: no prior skeletal-related event on treatment, prior skeletal-related event on treatment, no prior skeletal-related event off treatment, prior skeletal-related event off treatment, and death.

The model compared the cost effectiveness of denosumab with zoledronic acid, disodium pamidronate, ibandronic acid and best supportive care. Zoledronic acid was the primary comparator in patients with breast cancer, with disodium pamidronate and ibandronic acid as secondary comparators. In prostate cancer, for patients with no pain or pain with no prior skeletal-related event, the comparator was best supportive care, and in patients with pain and a prior skeletal-related event the comparator was zoledronic acid. In other solid tumours, for patients with no pain or pain with no prior skeletal-related event, the comparator was best supportive care and in patients with pain and a prior skeletal-related event the comparators were zoledronic acid and disodium pamidronate. The model had a 4-week cycle length and a half-cycle correction was applied. Patients were followed for 10 years.

The same model structure was used for each tumour type, but the absolute and relative risk of skeletal-related events, adverse events and cancer mortality were modelled to reflect the differences between tumour types. The skeletal-related event risk and event rates were derived from the individual denosumab clinical trials. Data from the zoledronic acid arm of each of the trials were used to estimate the baseline absolute risk of skeletal-related events. Treatment effects were estimated from the trial data for denosumab compared with zoledronic acid and from the network meta-analysis for the other comparators. Within each tumour type, all patients were assumed to have the same survival risk regardless of treatment. Five adverse events (osteonecrosis of the jaw, renal toxicity, hypercalcaemia, hypocalcaemia and skin infections) were included in the model based on their impact on cost and/or health-related quality of life. Adverse event data for denosumab and zoledronic acid were taken from the denosumab clinical trials, and for disodium pamidronate and ibandronic acid from published clinical trials. Discontinuation from treatment was based on the manufacturer’s phase III trial data and included discontinuation from adverse effects, withdrawal of consent, treatment refusal, protocol violation, other illnesses and other reasons. Discontinuation rates for other comparators were taken from the literature.

The utility values used in the model were derived from the denosumab clinical trials, which included the administration of the EQ-5D questionnaire every 4 weeks. For each skeletal-related event it was assumed that the utility decrement started 5 months before identification and resolved 5 months afterwards. All utility values were calculated separately for different tumour types. Utility values were provided academic-in-confidence by the manufacturer and cannot be reported in this document.

Drug costs were taken from BNF 61. Bisphosphonate and denosumab administration costs were derived from a structured questionnaire conducted among UK healthcare professionals and a subsequent costing study. It was assumed that bisphosphonates were administered every 4 weeks. Skeletal-related event costs were derived from a prospective observational study in the UK and cost estimation using NHS reference costs and personal social services costs. Monitoring and adverse events costs were based on NHS reference costs. In the base-case analysis it was assumed that vertebral fractures were asymptomatic and incurred no costs.

The manufacturer of denosumab has agreed a patient access scheme with the Department of Health, in which a discount on the list price of denosumab is offered. The size of the discount is commercial-in-confidence. The base-case results for the incremental cost per QALY gained without the patient access scheme and with the patient access scheme are presented.

For breast cancer, in the manufacturer’s base-case analysis without the patient access scheme, denosumab when compared with zoledronic acid was associated with an incremental cost of £1484 and an incremental QALY gain of 0.07 leading to an ICER of £203,387 per QALY gained. Denosumab was associated with an ICER of £13,835 per QALY gained when compared with ibandronic acid and dominated (that is, was less costly and more effective than) disodium pamidronate.

For breast cancer, in the manufacturer’s analysis with the patient access scheme, denosumab when compared with zoledronic acid was associated with a cost saving of £483 and an incremental QALY gain of 0.07. When compared with ibandronic acid and disodium pamidronate denosumab was associated with cost savings of £1895 and £3453 and incremental QALYs of 0.005 and 0.013 respectively. Denosumab therefore dominated each comparator.

For prostate cancer, in the manufacturer’s base-case analysis without the patient access scheme, in the subgroup of patients with painful bone metastases and who have experienced a prior skeletal-related event, denosumab when compared with zoledronic acid was associated with an incremental cost of £922 and an incremental QALY gain of 0.016 leading to an ICER of £573,276 per QALY gained. In the subgroup of patients with no pain or pain and no history of a prior skeletal-related event, denosumab when compared with best supportive care was associated with an incremental cost of £3993 and an incremental QALY gain of 0.039 leading to an ICER of £102,067 per QALY gained.

For prostate cancer, in the manufacturer’s analysis with the patient access scheme, in the subgroup of patients with painful bone metastases and who have experienced a prior skeletal-related event, denosumab when compared with zoledronic acid was associated with an incremental cost of £757 and an incremental QALY gain of 0.006. Denosumab therefore dominated zoledronic acid. In the subgroup of patients with no pain or pain and no history of a prior skeletal-related event, denosumab when compared with best supportive care was associated with an incremental cost of £2790 and an incremental QALY gain of 0.039 with an ICER of £71,320 per QALY gained.

For prostate cancer, in the manufacturer’s analysis with the patient access scheme, in the subgroup of patients with painful bone metastases and who have experienced a prior skeletal-related event, denosumab when compared with zoledronic acid was associated with a cost saving of £43 and an incremental QALY gain of 0.004 leading to an ICER of £205,580 per QALY gained. Denosumab dominated disodium pamidronate. In the subgroup of patients with no pain or pain and no history of a prior skeletal-related event, denosumab when compared with best supportive care was associated with an incremental cost of £2530 and an incremental QALY gain of 0.021 leading to an ICER of £122,499 per QALY gained.

For other solid tumours including non-small cell lung cancer, in the manufacturer’s base-case analysis without the patient access scheme, in the subgroup of patients with painful bone metastases and who have experienced a prior skeletal-related event, denosumab when compared with zoledronic acid was associated with a cost saving of £43 and an incremental QALY gain of 0.004. Denosumab therefore dominated zoledronic acid and disodium pamidronate. In the subgroup of patients with no pain or pain and no history of a prior skeletal-related event, denosumab when compared with best supportive care was associated with an incremental cost of £1730 and an incremental QALY gain of 0.021 leading to an ICER of £83,763 per QALY gained.

The manufacturer undertook sensitivity analyses to assess the impact of parameters and assumptions on the cost per QALY gained. The ICER was sensitive to skeletal-related event utilities, alternative dosing frequency and administration of bisphosphonates, application of skeletal-related event rates without the 21-day window, and assuming no discontinuation rate.

In the Assessment Group’s view the manufacturer’s model was of good quality and structure but noted that:

- Treatment-specific effect data for the subgroups based on prior skeletal-related event experience were not applied.
The rates of adverse events for best supportive care were assumed to be zero.
Costs for zoledronic acid used in the model were 5% higher than those listed in BNF 62.
The manufacturer used median values rather than means from the costing study because of the skewed nature of the replies.
The manufacturer used 2008–2009 reference costs for radiotherapy planning and administration rather than the 2009–2010 costs that were used for all other skeletal-related events.
There was no detail about the functional forms that were tested during the EQ-5D data analysis.

Assessment Group model

4.2.17 The Assessment Group rebuilt the manufacturer's model using the same basic structure. The Assessment Group included the same analyses as the manufacturer: breast cancer, prostate cancer and other solid tumours (including non-small cell lung cancer), but also included a separate analysis based on the subgroup data for people with non-small cell lung cancer. Analyses were completed including all patients, and separately for patients who had not had a skeletal-related event and those who had. There were no data to allow separation of non-small cell lung cancer outcomes by skeletal-related event history, therefore only an analysis of all patients is presented for this subgroup.

4.2.18 In the base-case analysis the Assessment Group applied the results of their network meta-analysis for time to first skeletal-related event and risk of subsequent skeletal-related event. In addition, the Assessment Group made amendments to the resource data, using the zoledronic acid price and the disodium pamidronate price based on BNF 62. They recalculated the costs associated with skeletal-related events, including excess bed days (except for spinal cord compression). The costs for serious adverse events were also amended to allow for some serious adverse events such as osteonecrosis of the jaw and renal toxicity to include some costs associated with outpatient care as well as inpatient care.

4.2.19 The results of the Assessment Group's base-case cost-effectiveness analysis without the patient access scheme showed that for breast cancer (analysis of all patients, regardless of skeletal-related event history), denosumab when compared with zoledronic acid was associated with an incremental cost of £1707 and an incremental QALY gain of 0.007 leading to an ICER of £245,264 per QALY gained. Denosumab was associated with a incremental cost of £6242 and incremental QALY gain of 0.027 giving an ICER of £229,547 per QALY gained when compared with best supportive care. When compared with disodium pamidronate, denosumab dominated with a cost saving of £1355 and incremental QALY gain of 0.012.

4.2.20 For breast cancer, the Assessment Group's analysis with the patient access scheme showed that denosumab when compared with zoledronic acid and disodium pamidronate was associated with cost savings of £243 and £3305 respectively and an incremental QALY gain of 0.007 and 0.012. Denosumab dominated zoledronic acid and disodium pamidronate. Compared with best supportive care denosumab was associated with an incremental cost of £4292 and an incremental QALY of 0.027 leading to an ICER of £157,829 per QALY gained.

4.2.21 For prostate cancer, in the Assessment Group's base-case analysis without the patient access scheme, in the subgroup of patients who have experienced a prior skeletal-related event, denosumab when compared with zoledronic acid was associated with an incremental cost of £1053 and an incremental QALY gain of 0.006 leading to an ICER of £170,854 per QALY gained. When compared with best supportive care, denosumab was associated with an incremental cost of £3897 and incremental QALY gain of 0.025 leading to an ICER of £152,916 per QALY gained. In the subgroup of patients with no prior skeletal-related event, denosumab when compared with zoledronic acid was associated with an incremental cost of £1061 and an incremental QALY gain of 0.011 giving an ICER of £99,561 per QALY gained. When compared with best supportive care, denosumab was associated with an incremental cost of £3969 and an incremental QALY gain of 0.039 leading to an ICER of £103,003 per QALY gained.

4.2.22 For prostate cancer, with the patient access scheme, in the subgroup of patients who have experienced a prior skeletal-related event, denosumab when compared with zoledronic acid was associated with a cost saving of £131 and an incremental QALY gain of 0.006. Denosumab was therefore dominant. Compared with best supportive care the incremental cost was £2713 and incremental QALY gain 0.025 leading to an ICER for denosumab of £106,446 per QALY gained. In the subgroup of patients with no prior skeletal-related event, denosumab when compared with zoledronic acid was associated with a cost saving of £123 and an incremental QALY gain of 0.011. Denosumab was therefore dominant. Compared with best supportive care the incremental cost was £2783 and incremental QALY gain 0.009 leading to an ICER for denosumab of £72,269 per QALY gained.

4.2.23 For other solid tumours including non-small cell lung cancer, in the Assessment Group's base-case analysis without the patient access scheme, in the subgroup of patients who have experienced a prior skeletal-related event, denosumab when compared with zoledronic acid was associated with an incremental cost of £848 and an incremental QALY gain of 0.004 leading to an ICER of £196,114 per QALY gained. When compared with best supportive care, denosumab was associated with an incremental cost of £2620 and an incremental QALY gain of 0.011 giving an ICER of £238,840 per QALY gained. In the subgroup of patients who have no prior skeletal-related event, denosumab when compared with zoledronic acid was associated with an incremental cost of £41 and an incremental QALY gain of 0.008 leading to an ICER of £229,547 per QALY gained. When compared with best supportive care, denosumab was associated with an incremental cost of £1583 and an incremental QALY gain of 0.012 leading to an ICER of £238,840 per QALY gained.

4.2.24 For other solid tumours including non-small cell lung cancer and including the patient access scheme, in the subgroup of patients who have experienced a prior skeletal-related event, denosumab when compared with zoledronic acid was associated with an incremental cost of £66 and an incremental QALY gain of 0.004 leading to an ICER of £15,282 per QALY gained. When compared with best supportive care denosumab was associated with an incremental cost of £1839 and an incremental QALY gain of 0.011 leading to an ICER of £167,587 per QALY gained. In the subgroup of patients who have no prior skeletal-related event denosumab when compared with zoledronic acid was associated with an incremental cost of £41 and an incremental QALY gain of 0.008 leading to an ICER of £15,282 per QALY gained. Compared with best supportive care, denosumab was associated with an additional cost of £1691 and an incremental QALY of 0.024 leading to an ICER of £70,679 per QALY gained.

4.2.25 The Assessment Group also presented an analysis for the patient group with non-small cell lung cancer. For this group (including both those with and without a prior skeletal-related event), without the patient access scheme, denosumab when compared with zoledronic acid was associated with an incremental cost of £708 and an incremental QALY gain of 0.005 leading to an ICER of £149,878 per QALY gained. When compared with best supportive care, denosumab was associated with an incremental cost of £2262 and an incremental QALY gain of 0.012 giving an ICER of £191,412 per QALY gained.

4.2.26 For non-small cell lung cancer with the patient access scheme, denosumab was associated with an incremental cost of £28 and an incremental QALY gain of 0.005 leading to an ICER of £5972. Compared with best supportive care, denosumab was associated with incremental costs of £1583 and an incremental QALY of 0.012 leading to an ICER of £133,926 per QALY gained.

4.2.27 The Assessment Group performed univariate sensitivity analyses to assess the impact of using some of the manufacturer's costs and estimates within the model, alternative rates of discontinuation assumed for active treatments, alternative assumptions...
about the change in utility for a patient who has never had a skeletal-related event having a skeletal-related event, applying utility multipliers for those nearing death, limiting or excluding the effects of serious adverse events, altering the time horizon to 5 years and to 2 years, excluding general mortality, and extending the effect of spinal cord compression to beyond 5 months from diagnosis. Analyses were also completed assuming alternative costs for zoledronic acid. Sensitivity analyses included the patient access scheme. The results of these analyses generally supported the conclusions in the base-case cost-effectiveness analysis

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of denosumab, having considered evidence on the nature of skeletal-related events in adults with bone metastases from solid tumours and the value placed on the benefits of denosumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.3.2 The Committee considered the nature of the condition, and noted evidence submitted and presented by the patient experts and clinical specialists on the impact on people of bone metastasis. The Committee heard from the clinical specialists and patient experts that complications from bone metastases can affect mobility so people can be housebound and unable to participate socially and have difficulties with employment. The Committee also heard that pain from bone metastasis can be significant and managing pain is an important part of treatment. Pain can be continuous and excruciating and sometimes means the patient needs hospitalisation. Pain treatment can include high-dose opioids, which can have undesirable effects such as sleepiness and constipation, which can severely affect some people. The clinical specialists and patient experts considered that treatments that delayed skeletal-related events and reduced pain enabled people to enjoy family life for longer. The Committee recognised the impact on people of bone metastases and the value placed by them on minimising the effects of bone metastases.

4.3.3 The Committee discussed the existing clinical options for preventing skeletal-related events in people with bone metastasis from breast cancer, noting that the guideline on advanced breast cancer (NICE clinical guideline 81) recommends using bisphosphonates. The Committee heard from clinical specialists that bisphosphonates are commonly used in this patient group, and that, of the available bisphosphonates, oral ibandronate may be preferred because it can be administered in the community. However, the Committee also heard that if people have acute pain, zoledronic acid or intravenous ibandronate are used. The Committee also heard that of the intravenous treatments zoledronic acid is normally used in people with bone metastasis from breast cancer. The Committee heard from the patient expert that not everyone with metastatic breast cancer prefers oral bisphosphonates over intravenous bisphosphonates because the administration requirements for oral treatment are complex and sometimes people prefer the more frequent clinical contact that is necessary with an intravenous drug. The Committee concluded that for people with bone metastases from breast cancer bisphosphonates were the appropriate comparator, specifically zoledronic acid and ibandronate.

4.3.4 The Committee discussed the existing clinical options for preventing skeletal-related events in people with bone metastasis from prostate cancer. The Committee heard from clinical specialists that bisphosphonate use is not uniform across the NHS in people with bone metastasis from prostate cancer. The Committee heard from clinical specialists that where zoledronic acid is used, it is used in accordance with the guideline on prostate cancer (NICE clinical guideline 58) in people with hormone-refractory (castration resistant) prostate cancer with painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed. The Committee noted comments received during consultation regarding zoledronic acid not being an appropriate comparator for denosumab, for the prevention of skeletal-related events in patients with metastatic prostate cancer. The Committee heard testimony from the NICE Director of the Centre for Clinical Practice, who was the Chair of the Guideline Development Group that developed the guideline on prostate cancer (NICE clinical guideline 58). The Committee heard that when the clinical guideline was being developed the group evaluated bisphosphonates both for preventing skeletal-related events and for pain relief from bone metastasis in hormone-refractory metastatic prostate cancer. The Committee understood that the group considered evidence from a systematic review and meta-analysis and, based on that evidence, did not recommend bisphosphonates for preventing skeletal-related events in prostate cancer. But the evidence did suggest a trend favouring bisphosphonates over placebo for relieving pain from bone metastases in prostate cancer. The Guideline Development Group therefore recommended bisphosphonates for a subgroup of patients with prostate cancer for whom the intention was to use them as pain relief. The Committee noted that neither denosumab nor any of the bisphosphonates has marketing authorisation for pain relief in this group and that pain relief on its own was not in this appraisal’s remit, which is limited by denosumab’s marketing authorisation to the prevention of skeletal-related events. The Committee concluded that because the intention of the guideline on prostate cancer (NICE clinical guideline 58) was to recommend bisphosphonates for pain relief, the appropriate comparator for patients with metastatic prostate cancer in an appraisal considering the prevention of skeletal-related events is best supportive care.

4.3.5 The Committee discussed the existing clinical options for preventing skeletal-related events in people with bone metastasis from solid tumours other than breast and prostate tumours. The Committee noted that no NICE guidelines or other guidelines had been identified with recommendations about using bisphosphonates in this patient group. The Committee noted that a patient chart review by the manufacturer estimated that in 50% of people with bone metastasis from other solid tumours, bisphosphonates were prescribed or planned for future use and zoledronic acid (80%) and disodium pamidronate (20%) are the bisphosphonates generally used in these patients. The Committee heard from the Assessment Group that they had been advised that oral bisphosphonates are not used in people with bone metastases from lung cancer, and clinical specialists advised that in renal cell carcinoma zoledronic acid may be used. The Committee concluded that there was uncertainty about the treatments in routine use for people with bone metastases from solid tumours other than breast or prostate. It accepted that intravenous bisphosphonates namely zoledronic acid and disodium pamidronate would be used for a proportion of people, and that based on the evidence of the manufacturer it was unlikely that bisphosphonates would be used as a first-line treatment. The Committee concluded therefore that the appropriate comparator for people with bone metastases from solid tumours other than breast or prostate were best supportive care in general, and zoledronic acid or disodium pamidronate for a proportion of patients in which they are prescribed in clinical practice.

4.3.6 The Committee discussed the perceived benefits of denosumab as a technology. It considered whether the subcutaneous route of administration offered advantages to patients or the NHS in terms of resource use in comparison with intravenous, though not oral, bisphosphonates. The Committee heard from the clinical specialist that, in theory, denosumab could be given at GPs’ surgeries and could free up resources from chemotherapy suites. It also heard that, in comparison with zoledronic acid, denosumab was considered to offer some benefits in terms of reduced nephrotoxicity and acute phase reactions (for example fever, muscle pain and bone pain, and arthralgia). It also heard that denosumab did not require blood test monitoring each month except in patients with severe renal impairment (creatinine clearance < 30 ml/min or receiving dialysis) to monitor hypocalcaemia, which would potentially make it more convenient for patients.

4.3.7 The Committee noted that the primary outcome measure in the denosumab trials was time to first on-study skeletal-related event. The Committee noted that skeletal-related event was a composite outcome indicator which included both treatments as well as complications of bone metastasis. The Committee discussed whether using a composite outcome was clinically meaningful. The Committee heard from clinical specialists that each component of the composite outcome was important but that to interpret the data,
it is helpful if different skeletal-related events are reported separately. However, clinical trials in bone metastasis have historically reported composite outcomes and there is no validated method to assign different weights to different events in the composite indicator. The Committee noted comments received in consultation about the uncertain clinical significance of using composite skeletal-related event outcomes, but concluded that it was appropriate to use skeletal-related events as defined in the clinical trials as the basis of its decision.

4.3.8 The Committee discussed the outcomes of the denosumab trials in the context of the other trials identified by the Assessment Group in their network meta-analysis. The Committee noted that the trials consistently showed that denosumab improved skeletal-related event outcomes compared with zoledronic acid, and that zoledronic acid improved skeletal-related event outcomes compared with placebo. The Committee discussed the other outcomes data from the denosumab trials noting that there were no benefits to overall survival for denosumab in comparison with zoledronic acid and that the outcomes for pain, although all favoured denosumab, were not all statistically significant. The Committee concluded that the evidence directly comparing denosumab with zoledronic acid for skeletal-related event outcomes suggested that denosumab was clinically more effective than zoledronic acid. However, the data for other outcomes such as pain, survival and quality of life did not show such a consistent benefit over zoledronic acid.

4.3.9 The Committee discussed the result of the Assessment Group’s network meta-analysis to compare denosumab with other bisphosphonates as well as best supportive care. The Committee noted that the Assessment Group had initially completed a random effects model, but subsequently preferred a fixed effects model. The Committee was aware that a fixed effects model is appropriate when it is believed that each study is estimating the same treatment effect or that inferences are to be made based on the available studies. The Committee discussed whether a random effects model would have been more appropriate for the network meta-analysis to account for heterogeneity among the included studies. The Committee heard from the Assessment Group that there were not enough studies included in the network meta-analysis for the between-study standard deviation to be properly calculated. It heard that an analysis that included an assumption of mild to moderate heterogeneity, although affecting the estimates of effect, would not have affected the outcomes of the economic modelling. The Committee further noted consultation comments received from the manufacturer about the appropriateness and reliability of the indirect method used to estimate the effect of zoledronic acid compared with disodium pamidronate, when direct estimation was possible. It noted that the Assessment Group accepted the comment made by the manufacturer and that they had revised their network meta-analysis in light of the manufacturer’s comment. The Committee noted the revised analysis and acknowledged the improvements made. The Committee agreed that there was consistency across the evidence sources submitted and that it could consider the analyses of cost effectiveness that had used the estimates from the Assessment Group’s network meta-analysis using the fixed effects model.

4.3.10 The Committee discussed the Assessment Group’s subgroup analysis of the data for patients with non-small cell lung cancer. The Committee heard from clinical specialists that they considered that this was an appropriate subgroup clinically because different primary tumour types responded to treatment in different ways. However, the Committee also recognised the comments from the manufacturer that these data were from a post-hoc analysis that was not powered to show a difference in effect. The Committee concluded that it was appropriate to consider subgroups based on primary tumour type. However, it was aware of the limitations of the data available to inform such analysis.

4.3.11 The Committee noted that in accordance with the final scope for the appraisal both the manufacturer and the Assessment Group had provided subgroup analyses based on patient history of prior skeletal-related event. The Committee discussed the analyses, noting that the evidence was generally consistent with the analysis that included all patients, but that in some cases the effect was no longer statistically significant. The Committee heard from the Assessment Group that this subgroup analysis was potentially important in the economic analysis because prior history influenced the baseline utility in the model, as well as the likelihood of having skeletal-related events. The Committee heard from the clinical specialists that they considered that history of a prior skeletal-related event reflected a continuation of disease progression rather than a separate subgroup. The Committee took account of these views when it considered the cost-effectiveness analysis. Based on the clinical evidence the Committee considered that the data were consistent regardless of prior skeletal-related event history.

4.3.12 The Committee discussed the adverse events data from the denosumab trials. The Committee noted that in the trials fewer incidents of renal toxicities and acute phase reactions were reported in the denosumab group than in the zoledronic acid group. However, there was a higher incidence of hypocalcaemia and osteonecrosis of the jaw in the denosumab group than in the zoledronic acid group. The Committee heard from clinical specialists that they considered that denosumab could be given to people with mild to moderate renal failure and that this could be particularly valuable for people with metastatic prostate cancer, many of whom have reduced renal function. The clinical specialists noted the paradox that such patients had not been able to be enrolled in the denosumab trials because zoledronic acid was used as a comparator. The Committee understood that denosumab may have a specific role in preventing skeletal-related events for people who cannot be treated with bisphosphonates because of reduced renal function.

Cost effectiveness

4.3.13 The Committee discussed the economic models provided by the manufacturer and the Assessment Group, noting that the Assessment Group had based its model on the basic structure of the manufacturer’s model. The Committee discussed the model structure and the parameter values used, noting where the Assessment Group had updated or amended inputs used by the manufacturer. It noted the similarities in the outputs of the modelling completed by the manufacturer and the Assessment Group, but it also noted the considerable differences in these outputs compared with those of the existing cost-effectiveness literature. The Committee concluded that the structure of the Assessment Group model was appropriate to inform its deliberations, but given the differences in outputs it was appropriate to also consider the wider economic evidence available.

4.3.14 The Committee discussed whether the assumption of a reduction in utility starting 5 months before the skeletal-related event is recorded is a valid assumption. The Committee heard from the clinical specialists that they would expect a gradual deterioration in the patient’s condition before a skeletal-related event happened, for example pain would start worsening before a patient would be considered for palliative radiotherapy or bone surgery. The Committee concluded that it was appropriate to assume reduced quality of life before the skeletal-related event happened.

4.3.15 The Committee noted that analyses had been completed for all patients, and separately for patients without a prior skeletal-related event and patients with a prior skeletal-related event. The Committee, having heard the experts’ view that this was not a distinction they made (see section 4.3.11), and having noted that the outputs of the modelling were consistent across these analyses, concluded that this was not an important subgroup for decision-making in this specific instance.

4.3.16 The Committee discussed the assumptions about the cost and adverse events modelled for best supportive care, noting that the model assumed there were no adverse events for best supportive care. The Committee discussed the nature of best supportive care for people with bone metastasis. The Committee heard from clinical specialists that opioid analgesia is the main form of pain control for people with bone metastasis. It heard that opioids have many adverse reactions including altered consciousness, sleepiness and constipation. The Committee also heard from the clinical specialists that radioactive isotopes are also increasingly used for pain control for people with bone metastasis from prostate cancer. The Committee concluded that the costs of best supportive care may have been under estimated in the model and that there could be additional disutilities resulting from adverse events that were not counted for in the model. However, no evidence had been provided that enabled it to quantify the impact of this
on cost effectiveness.

4.3.17 The Committee discussed the results of the Assessment Group analyses. The Committee noted that the modelling predicted a small incremental QALY gain (range from 0.004 to 0.011) favouring denosumab when compared with zoledronic acid. It also noted the slightly larger, but still small, increments when denosumab was compared with best supportive care (range from 0.011 to 0.039). The Committee recognised that a similar QALY gain for both denosumab and zoledronic acid was calculated from the manufacturer’s modelling, and that these small gains meant that the ICERs were sensitive to small changes in costs.

4.3.18 The Committee discussed the estimates of cost effectiveness from the Assessment Group analyses without the patient access scheme. It noted that the ICER for denosumab when compared with zoledronic acid was more than £200,000 per QALY gained for the metastatic breast cancer population, more than £100,000 per QALY gained for the metastatic prostate cancer population, and £100,000 per QALY gained for the metastatic colorectal cancer population. The Committee also discussed the Assessment Group’s analyses of denosumab compared with best supportive care noting that these were consistent with the manufacturer’s analyses. The Committee noted that even with the patient access scheme denosumab was associated with high ICERs, the lowest of which in the Assessment Group’s analyses remained above £70,000 per QALY gained. Therefore the Committee concluded that denosumab could not be recommended as a cost-effective use of NHS resources.

4.3.19 In response to the consultation comments and the Committee’s subsequent conclusion that best supportive care is the appropriate comparator for patients with metastatic prostate cancer (see section 4.3.4), and for most patients with solid tumours other than breast and prostate (see section 4.3.5) the Committee discussed the Assessment Group’s analyses of denosumab compared with best supportive care noting that these were consistent with the manufacturer’s analyses. The Committee noted that even with the patient access scheme denosumab was associated with high ICERs, the lowest of which in the Assessment Group’s analyses remained above £70,000 per QALY gained. Therefore the Committee concluded that denosumab could not be recommended as a cost-effective use of NHS resources for the prevention of skeletal-related events in patients with bone metastases from prostate cancer or in the general population of patients with bone metastases from solid tumours other than breast and prostate.

4.3.20 The Committee discussed the implications of the analyses in both the Assessment Group and the manufacturer models, that is, when the results were considered incrementally the small gains in QALYs and relatively larger increases in costs meant that zoledronic acid was not a cost-effective use of NHS resources. The Committee discussed whether this altered its conclusions (see section 4.3.3 and 4.3.5) on the appropriateness of using zoledronic acid as a comparator against which to assess the cost effectiveness of denosumab in patients with breast cancer and for the subgroup of patients with solid tumours other than breast and prostate cancer for whom bisphosphonates were used.

4.3.21 The Committee therefore discussed the systematic literature review of cost-effectiveness studies reported by the Assessment Group. The Committee noted that cost-effectiveness studies of the bisphosphonates reported a range of ICERs, most of which were relatively favourable to the bisphosphonates in general and to zoledronic acid in particular. None of these however were based on utility measurement consistent with NICE’s methods guide. The Committee particularly examined the results of the Health Technology Assessment (HTA) monograph that informed the guideline on advanced breast cancer (NICE clinical guideline 81) and produced an ICER of £1850 per QALY gained. The Committee heard from the Assessment Group that there were some differences between its model and the HTA monograph in the cost estimates used and that the HTA monograph included additional costs specific to pain and its management. The incidence of skeletal-related events was also higher in the HTA monograph and the utility decrement associated with each skeletal-related event was considerably greater. The Committee heard from the clinical specialists that the management of breast metastasis has changed, which could partly explain the lower event rates in the denosumab trials and Assessment Group modelling. The Committee agreed there was transparency in the analyses completed by the Assessment Group and had considerable concern that both the Assessment Group model and the manufacturer’s model suggested that zoledronic acid was not cost effective compared with best supportive care. However, it considered that the cost effectiveness of zoledronic acid in comparison with best supportive care should be subject to an appropriate review of clinical and cost effectiveness before definitive conclusions can be drawn. The scope of this appraisal limited the Committee to appraising the cost effectiveness of denosumab in comparison with zoledronic acid or best supportive care. The Committee however emphasised the need for a review of previous and current economic analyses.

4.3.22 The Committee then discussed the analyses in patients with breast cancer and solid tumours other than breast and prostate comparing denosumab with zoledronic acid that included the patient access scheme. It noted that for breast cancer the patient access scheme reduced the cost of denosumab so that it became less costly and more effective than zoledronic acid. The Committee also noted that in patients with bone metastasis from solid tumours other than in the breast and prostate, inclusion of the patient access scheme reduced the ICER for denosumab compared with zoledronic acid to less than £16,000 per QALY gained and to less than £6000 per QALY gained in the non-small cell lung cancer subgroup. The Committee recognised that the submitted cost-effectiveness analyses suggested that zoledronic acid was not cost effective when compared with best supportive care. However, in view of the contradictory results from the published economic evaluations, the recommendations about bisphosphonates in the guideline on advanced breast cancer (NICE clinical guideline 81), and the submitted evidence about the use of zoledronic acid in the NHS, the Committee was persuaded that zoledronic acid was an appropriate comparator against which to appraise denosumab for patients with breast cancer and the subgroup of people with solid tumours other than breast and prostate for whom zoledronic acid is indicated. On balance the Committee, while recognising the uncertainties over the cost effectiveness of zoledronic acid concluded that denosumab, based on current prices and with the patient access scheme, was shown to be cost effective compared with zoledronic acid (or other bisphosphonates in the case of metastatic breast cancer). Thus denosumab will be an additional option when zoledronic acid (or other bisphosphonates in the case of metastatic breast cancer) is used. For breast cancer this should be in accordance with the recommendations in the guideline on advanced breast cancer (NICE clinical guideline 81).

4.3.23 The Committee noted comments received at consultation about the use of disodium pamidronate in solid tumours other than breast and prostate. It discussed whether denosumab should be recommended as an alternative to disodium pamidronate. The Committee was aware that zoledronic acid is the only bisphosphonate that has marketing authorisation in this patient group but that data provided by the manufacturer indicated that disodium pamidronate is being prescribed in approximately 20% of the patients who are being treated or have been treated with a bisphosphonate (see section 4.3.5). The Committee was aware that there is no estimate of effectiveness for denosumab in comparison with disodium pamidronate in this patient group, but noted the availability of evidence from patients with breast cancer. The Committee also took into consideration the price of disodium pamidronate which is relatively favourable to the bisphosphonates in general and to zoledronic acid in particular. None of these however were based on utility measurement consistent with NICE’s methods guide. The Committee particularly examined the results of the Assessment Group’s analyses suggested that zoledronic acid was not a cost-effective use of NHS resources. The Committee discussed whether this altered its conclusions (see section 4.3.3 and 4.3.5) on the cost effectiveness of denosumab in comparison with zoledronic acid or best supportive care. The Committee however, emphasised the need for a review of previous and current economic analyses.

4.3.24 The Committee discussed the Assessment Group’s univariate sensitivity analysis. It noted that the ICER was sensitive to reductions in the price of zoledronic acid. The Committee was aware that zoledronic acid is due to come off patent in 2013 and that this may result in a reduced price for zoledronic acid because cheaper generic versions will be available. The Committee agreed that in that scenario the cost-effective analysis that it based its decision on would need to be revised. The Committee therefore agreed that the guidance should be considered for review in a year’s time.

4.3.25 The Committee noted comments from consultation on the Assessment Report that recommendations should be based on the
intention to treat with zoledronic acid, rather than the ability to treat with zoledronic acid. This was so that denosumab would be available to people for whom zoledronic acid would otherwise be appropriate, but who could not be treated with it because it was contraindicated because of impaired renal function. The Committee agreed that the recommendations should be based on the intention to treat with zoledronic acid.

4.3.26 The Committee discussed potential equalities issues, noting issues raised about gender and transgender in relation to breast and prostate cancer. The Committee also considered the comment received at consultation that the differences in the recommendations for prostate and breast cancer could be wrongly attributed to discrimination. The Committee gave particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, disability, religion or belief, sexual orientation, age, pregnancy and maternity. The Committee did not consider that the wording of the recommendations affected access to treatment by these groups.

Summary of Appraisal Committee’s key conclusions

<table>
<thead>
<tr>
<th>TAXXX</th>
<th>Appraisal title: Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours</th>
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<tr>
<td><strong>Key conclusion</strong></td>
<td>Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from breast cancer, if the manufacturer provides denosumab with the discount agreed in the patient access scheme.</td>
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<td></td>
<td>In patients with bone metastasis from breast cancer the patient access scheme reduced the cost of denosumab so that it became less costly and more effective than zoledronic acid.</td>
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<td></td>
<td>Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.</td>
<td>4.3.19</td>
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<td></td>
<td>In comparison with best supportive care denosumab was associated with high incremental cost-effectiveness ratios (ICERs) even with the patient access scheme, the lowest of which remained above £70,000 per quality-adjusted life year (QALY) gained.</td>
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<td>Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from solid tumours other than breast and prostate if zoledronic acid or disodium pamidronate would otherwise be prescribed for these patients and the manufacturer provides denosumab with the discount agreed in the patient access scheme.</td>
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<td></td>
<td>In patients with bone metastasis from solid tumours other than breast and prostate, the patient access scheme reduced the ICER for denosumab compared with zoledronic acid to less than £16,000 per QALY gained and to less than £8000 per QALY gained in the non-small cell lung cancer subgroup.</td>
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**Current practice**

**Clinical need of patients, including the availability of alternative treatments**

For people with bone metastases from breast cancer, bisphosphonates are the appropriate comparator, specifically zoledronic acid and ibandronate.

The appropriate comparator for denosumab in patients with metastatic prostate cancer in an appraisal considering the prevention of skeletal-related events is best supportive care.

The appropriate comparators for people with bone metastases from solid tumours other than breast or prostate were best supportive care in general, and zoledronic acid or disodium pamidronate for a proportion of patients in whom they are prescribed in clinical practice.

**The technology**

**Proposed benefits of the technology**

The Committee heard from the clinical specialist that, in theory, denosumab could be given at GPs’ surgeries and could free up resources from chemotherapy suites. It also heard that, in comparison with zoledronic acid, denosumab was considered to offer some benefits in terms of reduced nephrotoxicity and acute phase reactions. It also heard that denosumab did not require blood test monitoring each month except in patients with severe renal impairment (creatinine clearance < 30 ml/min or receiving dialysis) to monitor hypocalcaemia, which would potentially make it more convenient for patients.

**What is the position of the treatment in the pathway of care for the condition?**

The Committee considered denosumab as an alternative to bisphosphonates and as an alternative to best supportive care when bisphosphonates are not used.

**Adverse effects**

The Committee noted that in the denosumab trials fewer incidents of renal toxicities and acute phase reactions were reported in the denosumab group than in the zoledronic acid group. However, there was a higher incidence of hypocalcaemia and osteonecrosis of jaw in the denosumab group than in the zoledronic acid group.

The Committee understood that denosumab may have a specific role in preventing skeletal-related events for people who cannot be
**Evidence for clinical effectiveness**

| Availability, nature and quality of evidence | The primary endpoint in the clinical trials (time to first on-study skeletal-related events) was based on a composite outcome indicator (that is skeletal-related events) which included both treatments and complications of bone metastasis. Clinical specialists considered that each component of the outcome was important but that to interpret the results it is helpful if different skeletal-related events are reported separately. The Committee concluded that it was appropriate to use skeletal-related events as the basis of the decision. | 4.3.7 |

| Relevance to general clinical practice in the NHS | The generalisibility of the trial data to general clinical practice in the NHS was not an issue in this appraisal. | N/A |

| Uncertainties generated by the evidence | A number of network meta-analyses were submitted. The Committee agreed that there was consistency across the evidence sources submitted and that it could consider the estimates of cost effectiveness that had used the estimates from the Assessment Group's network meta-analysis using a fixed effects model. | 4.3.9 |

| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | The Committee concluded that it was appropriate to consider subgroups based on primary tumour type. However, it was aware of the limitations of the data available to inform such analysis. | 4.3.10 |

| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee concluded that the evidence directly comparing denosumab with zoledronic acid suggested that denosumab was more clinically effective than zoledronic acid in all three cancer groups for which there was trial evidence. However, the data for other outcomes such as pain, survival and quality of life did not show such a consistent benefit over zoledronic acid. | 4.3.8 |

**Evidence for cost effectiveness**

| Availability and nature of evidence | The Committee discussed the economic models provided by the manufacturer and the Assessment Group noting that the Assessment Group had based its model on the basic structure of the manufacturer’s model. The Committee concluded that the structure of the Assessment Group model was appropriate to inform its deliberations, but that it was appropriate to also consider the wider economic evidence available. | 4.3.13 |

| Uncertainties around and plausibility of assumptions and inputs in the economic model | The Committee noted the similarities in the outputs of the modelling completed by the manufacturer and the Assessment Group, but it also noted the considerable differences in these outputs compared with those of the existing cost-effectiveness literature. | 4.3.13 |

| Incorporation of health-related quality-of-life benefits and utility values | The Committee discussed whether the assumption of a reduction in utility starting 5 months before the skeletal-related event is recorded is a valid assumption. The Committee concluded that it was appropriate to assume reduced quality of life before the skeletal-related event happened. | 4.3.14 |

| Are there specific groups of people for whom the technology is particularly cost effective? | The Committee concluded that denosumab, based on current prices and with the patient access scheme, was shown to be cost-effective compared with zoledronic acid (or other bisphosphonates in the case of metastatic breast cancer). Thus denosumab would be an additional option when zoledronic acid (or other bisphosphonates in the case of metastatic breast cancer) would be used. | 4.3.22 |
For patients with bone metastases from solid tumours other than breast and prostate, the Committee also discussed the use of disodium pamidronate in clinical practice. Although it recognised that no estimate of efficacy was available for disodium pamidronate in this group. It also noted that its cost was higher than that of zoledronic acid. The Committee concluded that denosumab could also be considered an alternative to disodium pamidronate in patients with bone metastasis from solid tumours other than breast and prostate for whom it is currently being considered.

What are the key drivers of cost effectiveness?

The Committee discussed the univariate sensitivity analysis conducted by the Assessment Group. It noted that the ICER was sensitive to reductions in the price of zoledronic acid.

Most likely cost-effectiveness estimate (given as an ICER)

Without the patient access scheme denosumab could not be recommended as a cost-effective use of NHS resources.

For breast cancer the patient access scheme reduced the cost of denosumab so that it became less costly and more effective than zoledronic acid.

For patients with bone metastasis from solid tumours other than breast and prostate, the patient access scheme reduced the ICER for denosumab compared with zoledronic acid to less than £16,000 per QALY gained and to less than £6000 per QALY gained in the non-small cell lung cancer subgroup.

For all three patient groups, in comparison with best supportive care denosumab was associated with high ICERs even with the patient access scheme in the Assessment Group’s analyses, the lowest of which remained above £70,000 per QALY gained.

Additional factors taken into account

Patient access schemes (PPRS)

The manufacturer of denosumab has agreed a patient access scheme with the Department of Health, in which a discount on the list price of denosumab is offered. The size of the discount is commercial-in-confidence.

End-of-life considerations

End of life considerations were not addressed in this appraisal.

Equalities considerations and social value judgements

The Committee discussed potential equalities issues, noting issues raised about gender and transgender in relation to breast and prostate cancer. The Committee also considered the comment received at consultation that the differences in the recommendations for prostate and breast cancer could be wrongly attributed to discrimination. The Committee gave particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, disability, religion or belief, sexual orientation, age, pregnancy and maternity. The Committee did not consider that the wording of the recommendations affected access to treatment by these groups.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 The Department of Health and the manufacturer have agreed that denosumab will be available to the NHS with a patient access scheme in which a discount is applied to all invoices. The level of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate the level of discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme can be directed to the manufacturer at: NICE to include at time of publication

5.3 The technology in this appraisal may not be the only treatment for bone metastases from solid tumours recommended in NICE guidance, or otherwise available in the NHS. Therefore, if a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with section 5.1) when the clinician concludes and the patient agrees that the recommended technology is the most
appropriate to use, based on a discussion of all available treatments.

5.4 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

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

6 Related NICE guidance

Published

Under development
NICE is developing the following guidance (details available from www.nice.org.uk):
- Denosumab for prolonging bone metastasis-free survival in hormone-refractory prostate cancer. NICE technology appraisal guidance in development (publication expected November 2013).
- Prostate cancer: diagnosis and treatment (update). NICE clinical guideline in development (publication expected November 2013).

7 Review of guidance

7.1.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in July 2013. The Appraisal Committee noted that the ICER was sensitive to reductions in the price of zoledronic acid and was aware that zoledronic acid is due to come off patent in 2013 and that this may result in a reduction in the price of zoledronic acid because of the availability of cheaper generic versions. In that scenario the cost-effective analysis that it based its decision on would need to be revised.

7.1.2 NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee
May 2012

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

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett
Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler
Lay Member
Dr Mary Cooke
Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper
General Practitioner, St John’s Way Medical Centre, London

Professor Peter Crome
Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

Dr Christine Davey
Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York

Richard Devereaux-Phillips
Director, Public Policy and Advocacy NW Europe, BD, Oxford

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell
Consultant in Public Health, Bradford and Airedale Primary Care Trust

Professor Cathy Jackson
Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Professor Eugene Milne
Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Professor Katherine Payne
Professor of Health Economics, University of Manchester

Dr Danielle Preedy
Lay Member

Dr Martin Price
Head of Outcomes Research, Janssen-Cilag, Buckinghamshire

Alan Rigby
Senior Lecturer and Chartered Statistician, University of Hull

Dr Surinder Sethi
Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Dr John Stevens
Lecturer in Bayesian Statistics in Health Economics, School of Health and Related Research, Sheffield

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Judith Wardle
Lay Member

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

Anwar Jilani
Technical Lead(s)
Zoe Garrett
Technical Adviser
Lori Farrar
Project Manager

Appendix B: Sources of evidence considered by the Committee
A  The assessment report for this appraisal was prepared by Aberdeen HTA Group:

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:
- Amgen

II Professional/specialist and patient/carer groups:
- Breakthrough Breast Cancer
- Breast Cancer Care
- Macmillan Cancer Support
- Prostate Cancer Support Federation
- British Orthopaedic Oncology Society
- British Prostate Group
- British Psychosocial Oncology Society
- British Society for Haematology
- British Uro-Oncology Group
- Cancer Research UK
- Royal College of Nursing
- Royal College of Physicians

III Other consultees:
- Department of Health
- Welsh Government

IV Commentator organisations (without the right of appeal):
- British National Formulary
- Commissioning Support Appraisals Services
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Novartis
- British Prostate Group
- MRC Clinical Trials Unit
- Prostate Action
- Aberdeen Health Technology Assessment Group
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee’s deliberations. They gave their expert personal view on Denosumab for the treatment of bone metastases from solid tumours by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.
- Dr Amit Bahl, Consultant Clinical Oncologist, nominated by British Uro-oncology Group – clinical specialist
- Dr David Dodds, Consultant Oncologist, nominated by Healthcare Improvement Scotland (Gave last minute apologies to the Meeting) – clinical specialist
- Dr Stephen Harland, Consultant Medical Oncologist, nominated by Prostate Action – clinical specialist
- Tara Beaumont, Clinical Nurse Specialist, nominated by Breast Cancer Care – patient expert
- David Dodds, nominated by Prostate Cancer Support Federation (unfortunately unable to attend the meeting) – patient expert

D Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.
- Amgen