

Denosumab for the prevention of skeletal- related events in adults with bone metastases from solid tumours

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

Contents

1 Recommendations	4
2 Information about denosumab	5
3 Committee discussion	6
Clinical need and practice	6
Evidence and interpretation	7
4 Implementation.....	38
5 Appraisal Committee members and NICE project team.....	39
Appraisal Committee members	39
NICE project team	42
Sources of evidence considered by the Committee	42

1 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 and from solid tumours other than prostate if:
- bisphosphonates would otherwise be prescribed **and**
 - 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 Adults with bone metastases from solid tumours currently receiving denosumab for the prevention of skeletal-related events that is not recommended according to sections 1.1 and 1.2 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 Information about denosumab

- 2.1 Denosumab (XGEVA, Amgen) is a fully human monoclonal antibody that reduces osteoclast-mediated bone destruction by inhibiting the receptor activator of nuclear factor kappa-B ligand (RANKL), which is the primary mediator of increased osteoclast activity. Denosumab has a marketing authorisation for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours. The recommended dose of denosumab for the prevention of skeletal-related events in bone metastases from solid tumours is 120 mg every 4 weeks. It is administered as a single subcutaneous injection into the thigh, abdomen or upper arm.
- 2.2 The summary of product characteristics lists the following adverse reactions for denosumab: dyspnoea, diarrhoea, osteonecrosis of the jaw, hyperhidrosis, tooth extraction, hypophosphataemia and hypocalcaemia. Denosumab is contraindicated in people with severe, untreated hypocalcaemia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The cost of a 120-mg vial is £309.86 (excluding VAT; BNF 63). A year of treatment (13 doses) would cost £4,028.18 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts. 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 Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Committee discussion

Clinical need and practice

- 3.1 Bone is 1 of the most common sites for circulating cancer cells to settle and start growing. Metastases can occur in any bones in the body, but the spine is commonly affected, as well as the pelvis, hip, upper leg bones and the skull. Almost any cancer can metastasise to the bone, but cancers of the breast, prostate, lung, bladder, thyroid and kidney spread to the bone most often.
- 3.2 The manufacturer has estimated that there are more than 150,000 people in England and Wales with solid tumours and bone metastases, more than 80% of them with breast and prostate cancer. Approximately 0.5% of women with breast cancer have bone metastases at diagnosis and 4.7% develop bone metastases within 5 years. The manufacturer's submission reported that 11% of people with prostate cancer present with bone metastases at initial staging.
- 3.3 In women with breast cancer, bone metastases are associated with a median reduction in survival of approximately 2 years. In men with prostate cancer, bone metastases are associated with a reduced 5-year survival from 56% to 3%.
- 3.4 Bone metastases are also associated with reduced quality of life and an increased risk of complications from bone weakness or disrupted calcium homeostasis. Complications include pathological fractures (defined as pathological because minimal or no force is needed to cause them), spinal cord compression, radiation to the bone or surgery to the bone. These are collectively defined as skeletal-related events. Mobility may be reduced because of bone pain and other complications. Metastatic bone pain can be intermittent or constant, and people with bone metastases often report inadequate pain relief with analgesics.
- 3.5 The primary aim of treating bone metastases is to manage skeletal morbidity by delaying or preventing skeletal-related events. A second aim is to delay pain and reduce its severity. Current treatments for bone metastases and their complications include radiotherapy, orthopaedic surgery, bone-targeting radio-

pharmaceuticals and chemotherapy. Four bisphosphonates have a marketing authorisation for managing bone metastases or preventing skeletal-related events in people with solid tumours: zoledronic acid, disodium pamidronate, sodium clodronate and ibandronic acid. Zoledronic acid is the only bisphosphonate that has a marketing authorisation for the prevention of skeletal-related events in advanced malignancies involving bone without specifying the primary tumour type. Disodium pamidronate and sodium clodronate have a marketing authorisation for breast cancer and multiple myeloma, and ibandronic acid has a marketing authorisation for breast cancer only.

- 3.6 Management of bone metastases varies by primary cancer type. [NICE's guideline on advanced breast cancer](#) recommends offering bisphosphonates to people with newly diagnosed breast cancer and bone metastases to prevent skeletal-related events and reduce pain. NICE's previous guideline on prostate cancer (now replaced by [NICE's guideline on prostate cancer](#)) did not recommend the use of bisphosphonates to prevent or reduce complications of bone metastases in men with hormone refractory prostate cancer. In this patient group, bisphosphonates for pain relief may be considered when other treatments, including analgesics and palliative radiotherapy, have failed. The oral or intravenous route of administration should be chosen according to convenience, tolerability and cost. In people with lung cancer with bone metastases who need palliation and for whom standard analgesic treatments are inadequate, single-fraction radiotherapy was recommended in NICE's previous guideline on lung cancer (now replaced by [NICE's guideline on lung cancer](#)). NICE's previous guideline on metastatic spinal cord compression in adults (now replaced by [NICE's guideline on spinal metastases and metastatic spinal cord compression](#)) recommended bisphosphonates in people with breast cancer or multiple myeloma with vertebral involvement to reduce pain and the risk of vertebral fracture or collapse. In people with vertebral involvement from prostate cancer, bisphosphonates are recommended to reduce pain only if conventional analgesia fails to control pain.

Evidence and interpretation

The [Appraisal Committee](#) considered [evidence from a number of sources](#).

Clinical effectiveness

- 3.7 The Assessment Group identified 8 studies (including 3 of denosumab) reporting outcome data on skeletal-related events – 4 in patients with breast cancer, 2 in patients with prostate cancer and 2 in patients with other solid tumours. The 2 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.
- 3.8 The definition of skeletal-related event in some instances varied across the trials. In the denosumab trials, skeletal-related events was a composite outcome indicator that 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. Some trials also included hypercalcaemia or change in antineoplastic therapy in the definition of skeletal-related events. However, the definition of a skeletal-related event in the data informing the network meta-analysis was consistent across trials.

Breast cancer

- 3.9 A double-blind, randomised, controlled trial compared denosumab with zoledronic acid and enrolled patients (n=2,046) with confirmed breast cancer and at least 1 bone metastasis. Duration of follow-up was event rate driven and was approximately 34 months. The 3 other studies included in the network meta-analysis compared zoledronic acid with disodium pamidronate (n=1,130), zoledronic acid with placebo (n=228) and disodium pamidronate with placebo (n=754).
- 3.10 In the trial comparing denosumab with zoledronic acid, the median time to first skeletal-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). The study comparing zoledronic acid with placebo reported that median time to first skeletal-related event was not reached in the zoledronic acid group compared with 364 days in the placebo

group ($p=0.007$). Disodium pamidronate was also associated with a statistically significantly longer median time to first skeletal-related event than placebo (12.7 months compared with 7.0 months, $p<0.001$). The study comparing zoledronic acid with disodium pamidronate reported a statistically significant difference favouring zoledronic acid for time to first skeletal-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, $p=0.826$).

- 3.11 In the trial comparing denosumab with zoledronic acid, the risk of first and subsequent skeletal-related events was reduced in the denosumab group compared with the zoledronic acid group (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 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). The study comparing zoledronic acid and disodium pamidronate showed a statistically significant effect favouring zoledronic acid (RR 0.80, 95% CI 0.66 to 0.97).
- 3.12 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, $p<0.001$).
- 3.13 Results of the network meta-analysis showed that denosumab was associated with a statistically significant improvement compared with placebo for time to first on-study skeletal-related event (HR 0.46, 95% CI 0.29 to 0.72), risk of first and subsequent skeletal-related events (RR 0.45, 95% CI 0.28 to 0.72), and skeletal morbidity rate (RR 0.47, 95% CI 0.25 to 0.67). Denosumab was also associated with a statistically significant improvement compared with disodium pamidronate in the time to first skeletal-related event (HR 0.73, 95% CI 0.56 to 0.94) and the risk of first and subsequent skeletal-related events (RR 0.62, 95% CI 0.48 to 0.80). 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 event (HR 0.82, 95% CI 0.71 to 0.95) and the risk of first and subsequent skeletal-related events (RR 0.77, 95% CI 0.66 to 0.89), although the difference in skeletal morbidity rate was not statistically significant.

- 3.14 The denosumab trial reported no statistically significant difference in median overall survival for the denosumab group compared with the zoledronic acid group (HR 0.95, 95% CI 0.81 to 1.11, $p=0.49$).
- 3.15 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.
- 3.16 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 respectively. The rate of osteonecrosis of the jaw was similar in 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). 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

- 3.17 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 1 bone metastasis ($n=1,901$). Follow-up was 41 months. A further randomised controlled trial was included in the network meta-analysis that compared zoledronic acid with placebo ($n=643$).

- 3.18 In the trial comparing denosumab with zoledronic acid, median time to first on-study skeletal-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 event (488 days compared with 321 days, $p=0.009$).
- 3.19 In the trial comparing denosumab with zoledronic acid, the risk of developing first and subsequent on-study skeletal-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 comparing zoledronic acid with placebo, zoledronic acid was shown to reduce the risk of first and subsequent skeletal-related events (RR 0.64, 95% CI not reported, $p=0.002$).
- 3.20 In the trial comparing denosumab with zoledronic acid, skeletal morbidity rate was slightly 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 ($p=0.006$).
- 3.21 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 event (HR 0.56, 95% CI 0.40 to 0.77), risk of first and subsequent skeletal-related events (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 event (HR 0.82, 95% CI 0.71 to 0.95) and the risk of first and subsequent skeletal-related events (RR 0.82, 95% CI 0.71 to 0.94). The result for skeletal morbidity rate was not statistically significant.
- 3.22 In the trial comparing denosumab with zoledronic acid, median overall survival was similar in the denosumab group (19.4 months) and the zoledronic acid group (19.8 months, HR 1.03, 95% CI 0.91 to 1.17, $p=0.65$).
- 3.23 In the same trial, denosumab was associated with an approximately 1 month

longer duration to development of moderate or severe pain in patients with no or mild pain at baseline than zoledronic acid (median 5.8 compared with 4.9 months), although 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 analgesic use.

- 3.24 In the trial comparing denosumab with zoledronic acid, the incidences 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% [121 out of 943] compared with 6% [55 out of 945]). A greater number of patients in the denosumab group than the zoledronic acid group experienced osteonecrosis of the jaw (2% compared with 1%). A similar rate of adverse events potentially associated with renal impairment occurred in the denosumab group and the zoledronic acid group (15% and 16% respectively). During the first 3 days of treatment, fewer patients experienced symptoms associated with acute phase reactions in the denosumab group (8%) than the zoledronic acid group (18%).

Other solid tumours (including non-small-cell lung cancer)

- 3.25 A double-blind, randomised, controlled study compared denosumab with zoledronic acid and enrolled patients aged 18 years or older with confirmed solid tumours (except breast and prostate) or multiple myeloma ($n=1,776$). In the study, 40% of patients had non-small-cell lung cancer, 10% had multiple myeloma and 50% had other tumours. A post-hoc analysis of data from this study for other solid tumours, excluding multiple myeloma, ($n=1,597$) was provided by the manufacturer as academic-in-confidence and cannot be reported in this document. A summary of the publicly available data (that is, data including patients with multiple myeloma) is included in this document. Another study in patients with other solid tumours, excluding breast cancer and prostate cancer, ($n=507$) that compared zoledronic acid with placebo was included in the network meta-analysis.
- 3.26 In the trial comparing denosumab with zoledronic acid, the median time to first on-study skeletal-related event was longer for denosumab than zoledronic acid

- (20.6 compared with 16.3 months, HR 0.84, 95% CI 0.71 to 0.98, $p=0.0007$ non-inferiority). The study comparing zoledronic acid with placebo reported a statistically significant improvement in time to first on-study skeletal-related event (230 days compared with 163 days, $p=0.023$).
- 3.27 In the trial comparing denosumab with zoledronic acid, denosumab reduced the risk of developing first and subsequent skeletal-related events compared with zoledronic acid (RR 0.90, 95% CI 0.77 to 1.04, $p=0.14$). In the study comparing zoledronic acid with placebo, zoledronic acid also reduced the risk of developing first and subsequent skeletal-related events compared with placebo (HR 0.732, $p=0.017$).
- 3.28 The results of the network meta-analysis (using data that excluded patients with multiple myeloma) showed a statistically significant improvement with denosumab compared with placebo in time to first skeletal-related event (HR 0.49, 95% CI 0.30 to 0.78), risk of first and subsequent skeletal-related events (RR 0.62, 95% CI 0.46 to 0.85) and proportion of patients with on-study skeletal-related event (odds ratio [OR] 0.58, 95% CI 0.02 to 19.48). Denosumab was also associated with a statistically significant improvement compared with zoledronic acid in time to first skeletal-related event (HR 0.81, 95% CI 0.68 to 0.96). The difference for risk of first or subsequent skeletal-related events, and the proportion of patients with on-study skeletal-related events, was not statistically significant.
- 3.29 In the trial comparing denosumab with zoledronic acid, median overall survival was similar in both groups.
- 3.30 In the same trial, in patients with no or mild pain at baseline, time to development of moderate or severe pain was longer for denosumab than zoledronic acid (median 144 days compared with 112 days (HR 0.81, 95% CI 0.66 to 1.00, $p=0.049$). There were no differences in EQ-5D scores or analgesic use.
- 3.31 In the study comparing denosumab with zoledronic acid, serious adverse events were reported in 66% of patients treated with zoledronic acid and in 63% of patients treated with denosumab. Other adverse events were similar in both groups. Hypocalcaemia was reported in 10% of patients in the denosumab group and 5.8% of patients in the zoledronic acid group. Rates of osteonecrosis of the

jaw were similar in the denosumab (1.3%) and zoledronic acid (1.1%) groups. Renal adverse events occurred more often in the zoledronic acid group (10.9%) than the denosumab group (8.3%). Acute-phase reactions occurred more frequently in the zoledronic acid group (14.5%) than in the denosumab group (6.9%).

Non-small-cell lung cancer

- 3.32 The trial comparing denosumab with zoledronic acid in other solid tumours also reported data on a subgroup of patients with non-small-cell lung cancer (n=702). Denosumab was associated with delayed time to first on-study skeletal-related event in patients with non-small-cell lung cancer (HR 0.84, 95% CI 0.64 to 1.10, p=0.20). An ad hoc analysis for overall survival reported that denosumab improved overall survival relative to zoledronic acid by 21% in this patient group (HR 0.79, 95% CI 0.65 to 0.95). Skeletal morbidity rate, pain and health-related quality of life, and data on adverse events were not available separately for the non-small-cell lung cancer group. Other data were provided as academic-in-confidence by the manufacturer and cannot be included in this document.
- 3.33 The network meta-analysis included another study comparing zoledronic acid with placebo, in patients with solid tumours other than breast and prostate, that reported data separately for a subgroup of patients with non-small-cell lung cancer (n=244). Zoledronic acid was not associated with a statistically significant difference in time to first skeletal-related event compared with placebo (171 days and 151 days respectively, p=0.188) nor risk of first and subsequent skeletal-related events (HR 0.73, p=0.061). The incidence of skeletal-related events was lower in the zoledronic acid group (42% with an event), compared with placebo (45% with an event, p=0.557).
- 3.34 The results of the network meta-analysis showed that, compared with placebo, denosumab reduced the risk of first and subsequent skeletal-related events (RR 0.63, 95% CI 0.42 to 0.97). The difference in time to first skeletal-related event, and proportion of patients with a skeletal-related event, was not statistically significant. Compared with zoledronic acid none of the differences for time to first skeletal-related event, risk of first and subsequent skeletal-related event, and proportion of patients with a skeletal-related event was statistically significant.

Cost effectiveness

- 3.35 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 7 were cost-utility analyses. Of the 12 papers, 8 were in breast cancer, 2 in prostate cancer, 1 in lung cancer and 1 in renal carcinoma. The Assessment Group identified 11 studies, 1 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.
- 3.36 Of the 11 studies identified by the Assessment Group, 7 were in breast cancer, 3 in prostate cancer and 1 in lung cancer. Three of the breast cancer studies compared disodium pamidronate with best supportive care and reported incremental cost-effectiveness ratios (ICERs) for disodium pamidronate of between £1,851 and £276,444 per quality-adjusted life year (QALY) gained. One of the breast cancer studies compared zoledronic acid with best supportive care and reported that zoledronic acid was cost saving. The 3 other breast cancer studies compared different bisphosphonates, 2 reported that oral ibandronate was cost saving compared with zoledronic acid and disodium pamidronate, while the third reported that disodium pamidronate was cost saving compared with zoledronic acid. Of the 3 studies in prostate cancer, 1 compared zoledronic acid with best supportive care and reported ICERs for zoledronic acid of between £2,124 and £31,476 per QALY gained depending on the country of the cost data. The second reported that zoledronic acid was associated with £11,137 in additional costs per skeletal-related event avoided and had an ICER of £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 cost saving compared with best supportive care.
- 3.37 The manufacturer of denosumab submitted a Markov economic model that assessed the cost effectiveness of denosumab in 3 patient groups: breast cancer, prostate cancer and other solid tumours (excluding breast and prostate). The model had 5 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 had a 4-week

cycle length and a half-cycle correction was applied. Patients were followed for 10 years.

- 3.38 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. In patients with pain and a prior skeletal-related event, the comparators were zoledronic acid and disodium pamidronate.
- 3.39 The selection of the comparator in the analyses (that is best supportive care or a bisphosphonate) was informed by a chart review of patients in the UK. This showed that 87%, 49% and 37% of patients with bone metastases from breast, prostate and solid tumours other than breast and prostate were being treated or had been treated with bisphosphonates respectively. The choice of bisphosphonate in the analyses was informed by data from the IMS Oncology Analyzer. This reported that, for breast cancer, prostate cancer and other solid tumours, zoledronic acid was used in 50%, 92% and 80% of patients respectively. For disodium pamidronate, the proportions were 18%, 4% and 20% and, for ibandronic acid, the proportions were 31%, 4% and 0%.
- 3.40 The same model structure was used for each tumour type, but the absolute and relative risks 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 3 trial data and included discontinuation because of adverse effects, withdrawal of consent, treatment refusal, protocol violation, other illnesses and other reasons. Discontinuation rates for other comparators were taken from the literature.

- 3.41 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.
- 3.42 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.
- 3.43 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.

Analyses without the patient access scheme

- 3.44 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 £1,484 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.

- 3.45 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 0.006 leading to an ICER of £157,276 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 £3,993 and an incremental QALY gain of 0.039 leading to an ICER of £102,067 per QALY gained.
- 3.46 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 an incremental cost of £757 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 £2,530 and an incremental QALY gain of 0.021 leading to an ICER of £122,499 per QALY gained.

Analyses with the patient access scheme

- 3.47 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 £1,895 and £3,453 and incremental QALYs of 0.005 and 0.013 respectively. Denosumab therefore dominated each comparator.

- 3.48 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 £281 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 £2,790 and an incremental QALY gain of 0.039 with an ICER of £71,320 per QALY gained.
- 3.49 For other solid tumours including non-small-cell lung 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 and disodium pamidronate was associated with cost savings of £43 and £2,918, and incremental QALY gains of 0.004 and 0.006 respectively. 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 £1,730 and an incremental QALY of 0.021 leading to an ICER of £83,763 per QALY gained.
- 3.50 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.
- 3.51 In the Assessment Group's view, the manufacturer's model was of good quality and structure but noted that:
- Treatment-specific effects 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 to 2009 reference costs for radiotherapy planning and administration rather than the 2009 to 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

- 3.52 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 patients 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.
- 3.53 In the base-case analysis, the Assessment Group applied the results of its 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. It recalculated the costs associated with skeletal-related events, excluding 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.

Analyses without the patient access scheme

- 3.54 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 £1,707 and an incremental QALY gain of 0.007 leading to an ICER of £245,264 per QALY gained. Denosumab was associated with an incremental cost of £6,242 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 was dominant with a cost saving of £1,355 and incremental QALY gain of 0.012.
- 3.55 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 £1,053 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 £3,897 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 £1,061 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 £3,969 and an incremental QALY gain of 0.039 leading to an ICER of £103,003 per QALY gained.
- 3.56 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 £2,620 and an incremental QALY gain of 0.011 giving an ICER of £238,840 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 £823 and an incremental QALY gain of 0.008 leading to an ICER of £106,812 per QALY gained. When compared

with best supportive care, denosumab was associated with an incremental cost of £2,473 and an incremental QALY gain of 0.024 giving an ICER of £103,350 per QALY gained.

For the subgroup data for non-small-cell lung cancer (including both patients 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 £2,262 and an incremental QALY gain of 0.012 giving an ICER of £191,412 per QALY gained.

Analyses with the patient access scheme

- 3.57 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 £3,305 and an incremental QALY gain of 0.007 and 0.012 respectively. Denosumab dominated zoledronic acid and disodium pamidronate. Compared with best supportive care, denosumab was associated with an incremental cost of £4,292 and an incremental QALY of 0.027 leading to an ICER of £157,829 per QALY gained.
- 3.58 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 £2,713 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 £2,785 and incremental QALY gain 0.039 leading to an ICER for denosumab of £72,269 per QALY gained.
- 3.59 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 £1,839 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 £5,337 per QALY gained. Compared with best supportive care, denosumab was associated with an additional cost of £1,691 and an incremental QALY of 0.024 leading to an ICER of £70,679 per QALY gained.

- 3.60 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 £5,972. Compared with best supportive care, denosumab was associated with incremental costs of £1,583 and an incremental QALY gain of 0.012 leading to an ICER of £133,926 per QALY gained.
- 3.61 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 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.
- 3.62 After the consultation, additional information was provided about the use of bisphosphonates in patients with bone metastases from prostate cancer. The patient chart review (see section 3.39) included 1,161 patients with bone metastases from prostate cancer. In patients who were receiving or hsecad received bisphosphonate treatment (49%), the reasons for treatment (not mutually exclusive) were: to prevent skeletal-related events (56%), to treat or prevent bone pain (42%), to treat bone metastases or lesions at the original site

(27%), to prevent new bone metastases or lesions (21%), or because the patient had high-risk disease (18%). A survey of UK specialists who treat genitourinary cancer as a special or main interest was also submitted from the British Uro-Oncology Group. The survey was sent to 200 specialists, of whom 61 responded. Of those responding, 87% prescribed zoledronic acid, of whom 36% used it only in patients who had previously had a skeletal-related event. In patients who had had a prior skeletal-related event, 47% of specialists prescribed it mostly for bone pain, 32% prescribed it mostly for delaying further skeletal-related events and 17% prescribed it for both.

Consideration of the evidence

3.63 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

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

- 3.65 The Committee discussed the existing clinical options for preventing skeletal-related events in people with bone metastases from breast cancer, noting that [NICE's guideline on advanced breast cancer](#) 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 heard that, if there are concerns about adherence or 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 metastases 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.
- 3.66 The Committee then discussed the appropriate comparator for the group of people with bone metastases from prostate cancer. It discussed the recommendations in NICE's guideline on prostate cancer (now replaced by [NICE's guideline on prostate cancer](#)) and noted that bisphosphonates are not recommended for the prevention of skeletal-related events. However, for a subgroup of people with prostate cancer, bisphosphonates are recommended for use as pain relief when other treatments have failed. The Committee heard from a representative of the Guideline Development Group that the group evaluated bisphosphonates both for preventing skeletal-related events and for pain relief from bone metastases 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. However, the evidence did suggest a trend favouring bisphosphonates over placebo for relieving pain from bone metastases in prostate cancer. The Committee noted comments received during consultation that the systematic

review informing the guideline was 'flawed' because it assumed a class effect for bisphosphonates and included studies that were not relevant to the aim of preventing skeletal-related events. The Committee was aware that it was not within the remit of this appraisal to review the guideline recommendations, and that the analysis by both the manufacturer and the Assessment Group for this appraisal of denosumab had not assumed a class effect and had focused on studies with skeletal-related event outcomes. The Committee understood that, based on the guideline recommendations, bisphosphonates may be used in people with hormone-refractory (castration-resistant) prostate cancer. However, this use is restricted to pain relief when other treatments have failed.

3.67 The Committee noted that neither denosumab nor any of the bisphosphonates has marketing authorisation specifically for pain relief in people with prostate cancer. The Committee also noted the testimony from patient experts about the importance of pain relief (section 3.64). It discussed comments received during consultation that pain relief is an implicit part of preventing skeletal-related events because 1 of the events included in the skeletal-related event outcome is time to radiotherapy to the bone; an intervention given as pain relief. The Committee considered that there were differences between treatment aims to relieve pain, prevent pain and delay worsening pain, but understood that both were important to patients. However, the Committee was only able to make a recommendation in accordance with the wording of the marketing authorisation about the use of denosumab for the prevention of skeletal-related events. It was unable to make recommendations specifically for the use of denosumab for pain relief in people with prostate cancer.

3.68 The Committee then discussed the evidence about the use of bisphosphonates in UK clinical practice. The Committee heard from clinical specialists at the first Committee meeting that bisphosphonate use in people with bone metastases from prostate cancer is not uniform across the NHS. If zoledronic acid is used, it is used in people with castration-resistant (previously known as hormone-refractory) prostate cancer with painful bone metastases for whom other treatments, including analgesics and palliative radiotherapy, have failed. The Committee discussed the survey data and chart review data submitted by consultees. The Committee noted that these showed that bisphosphonates were being used in clinical practice, but that there was variation in reasons for their use. The Committee noted that the survey data had a high non-response rate

that could affect the reliability of the data and overestimate the use of bisphosphonates. The Committee also noted that the evidence identified by the Assessment Group for the effectiveness of bisphosphonates in comparison with standard care was the same randomised controlled trial as had been identified by the Guideline Development Group. In the absence of new data on the clinical effectiveness of bisphosphonates, the Committee was not persuaded that these data on use should be relied on over the recommendations in the guideline. The Committee concluded that, because bisphosphonates are recommended for pain relief when other treatments have failed in NICE's guideline on prostate cancer (now replaced by [NICE's guideline on prostate cancer](#)), and not for the prevention of skeletal-related events, the appropriate comparator in this appraisal for people with bone metastases from prostate cancer is best supportive care.

3.69 The Committee discussed the existing clinical options for preventing skeletal-related events in people with bone metastases from solid tumours other than breast and prostate tumours. The Committee noted that no NICE guidelines or other guidelines had been identified about using bisphosphonates in this patient group, and so guideline recommendations could not be used to inform the decision about the appropriate comparator. The Committee noted that a patient chart review by the manufacturer estimated that, in 50% of people with bone metastases 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 (see section 3.39). The Committee heard from the Assessment Group that it had been advised that oral bisphosphonates are not used in people with bone metastases from lung cancer, and the 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 and prostate. It accepted that intravenous bisphosphonates, namely zoledronic acid and disodium pamidronate, would be used for some people and that, based on the manufacturer's evidence, it was unlikely that bisphosphonates would be used as a first-line treatment. The Committee concluded that the appropriate comparators for people with bone metastases from solid tumours other than breast or prostate were best supportive care in general, and bisphosphonates, specifically zoledronic acid or disodium pamidronate for some patients for whom they are prescribed in clinical practice.

- 3.70 The Committee discussed the 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 compared with intravenous, though not oral, bisphosphonates. The Committee heard from the clinical specialists that, in theory, denosumab could be given at GP surgeries and could free up resources from chemotherapy suites. It also heard that, compared with zoledronic acid, denosumab was considered to offer some benefits in terms of reduced nephrotoxicity and acute phase reactions (for example, fever, muscle and bone pain, and arthralgia). It also heard that people having denosumab did not need blood test monitoring each month except those with severe renal impairment (creatinine clearance less than 30 ml/min or receiving dialysis) to monitor hypocalcaemia, which would potentially make it more convenient for people.
- 3.71 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 that included treatments as well as complications of bone metastases. The Committee discussed whether using a composite outcome was clinically meaningful. The Committee heard from the 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 metastases 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 during 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.
- 3.72 The Committee discussed the outcomes of the denosumab trials in the context of the other trials identified by the Assessment Group in its 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 outcome data from the denosumab trials, noting that there were no benefits to overall survival for denosumab compared 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.

- 3.73 The Committee discussed the result of the Assessment Group's network meta-analysis to compare denosumab with other bisphosphonates and best supportive care. The Committee noted that the Assessment Group had first 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 it had revised its network meta-analysis in light of the manufacturer's comment. The Committee noted the revised analysis and accepted this amendment considering that it did not materially affect the estimates produced. The Committee agreed that the estimates of the effects were consistent 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.
- 3.74 The Committee discussed the adverse events data from the denosumab trials. The Committee noted that 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 the 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 Committee noted comments from consultation 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 understood from clinical specialists that such people 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. The Committee agreed that the recommendations should be based on the intention to treat with bisphosphonates.

- 3.75 The Committee discussed the Assessment Group's subgroup analysis of the data for patients with non-small-cell lung cancer. The Committee heard from the 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.
- 3.76 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.

Cost effectiveness

- 3.77 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 (sections 3.35 and 3.36). 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.
- 3.78 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 in reflecting the clinical development of a skeletal-related event. 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 and accepted the 5-month utility reduction as plausible.
- 3.79 The Committee noted that analyses had been completed for all patients and separately using treatment-specific data for patients with and without a prior skeletal-related event. The Committee had heard from the clinical specialists that

this was not a distinction they made (see section 3.76), and noted that the outputs of the modelling were consistent across these analyses regardless of the data used. The Committee concluded that issues about the use in the modelling of subgroup-specific effects data based on prior skeletal-related event experience was not an important driver for decision-making.

- 3.80 The Committee discussed the assumptions about the cost and adverse events modelled for best supportive care in the manufacturer's and the Assessment Group's models, noting that both of the models assumed there were no adverse events for best supportive care. The Committee discussed the nature of best supportive care for people with bone metastases. The Committee heard from clinical specialists that opioid analgesia is the main form of pain control for people with bone metastases. 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 metastases from prostate cancer. The Committee noted that no evidence had been provided that enabled it to quantify the impact of this on cost effectiveness. The Committee concluded that the costs of best supportive care may have been underestimated, and that there could be additional disutilities resulting from adverse events that were not accounted for in the model.
- 3.81 The Committee discussed the results of the Assessment Group analyses. The Committee noted that depending on tumour type and skeletal related event history, the base-case analyses 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 QALY gains meant that the ICERs were sensitive to small changes in costs.
- 3.82 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 people with bone metastases from solid tumours other than breast and prostate. For denosumab compared with best supportive care, the ICERs were all more than £100,000 per QALY gained. The Committee recognised that the ICERs provided by the manufacturer for denosumab compared with zoledronic acid and denosumab compared with best supportive care were of a similar magnitude. The Committee concluded that without the patient access scheme denosumab could not be recommended as a cost-effective use of NHS resources.

- 3.83 The Committee discussed the implications of the analyses in both the Assessment Group and the manufacturer models, that is, when the interventions (that is denosumab, zoledronic acid and best supportive care) were considered simultaneously in an incremental analysis, 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 changed its conclusions (see sections 3.65 and 3.69) on the appropriateness of using zoledronic acid as a comparator against which to assess the cost effectiveness of denosumab in people with breast cancer and for the subgroup of people with solid tumours other than breast and prostate cancer for whom bisphosphonates are used.
- 3.84 The Committee noted that in the systematic literature review of cost-effectiveness studies reported by the Assessment Group, the 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. However, none of these studies was based on utility measurement consistent with [NICE's guide to the methods of technology appraisal](#). The Committee particularly examined the results of the Health Technology Assessment (HTA) monograph that informed [NICE's guideline on advanced breast cancer](#) and produced an ICER of £1,850 per QALY gained. The Committee heard from the Assessment Group that there were 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 that were not included in the Assessment Group model. 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 bone metastases has changed over

time as treatments have improved, which could partly explain the lower event rates in the denosumab trials and Assessment Group modelling in the current appraisal. The Committee agreed there was transparency in the modelling completed by the Assessment Group. The Committee expressed 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, the Committee recognised that the scope of this appraisal was limited to appraising the cost effectiveness of denosumab compared with zoledronic acid or best supportive care. It considered that the cost effectiveness of zoledronic acid compared with best supportive care would need to be subject to an appropriate review before definitive conclusions could be drawn.

- 3.85 The Committee then discussed the analyses in patients with breast cancer and solid tumours other than breast and prostate, comparing denosumab with zoledronic acid, including 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 people with bone metastases from solid tumours other than in the breast and prostate, including 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 £6,000 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, and the recommendations about bisphosphonates in [NICE's guideline on advanced breast cancer](#), the Committee was persuaded that zoledronic acid was an appropriate comparator against which to appraise denosumab for people 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). Therefore, denosumab should 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 NICE's guideline on advanced breast cancer.

- 3.86 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. The Committee concluded that denosumab could not be recommended as a cost-effective use of NHS resources for preventing skeletal-related events for those groups for whom best supportive care is the appropriate comparator (see sections 3.68 and 3.69), that is, people with bone metastases from prostate cancer and in the general population of people with bone metastases from solid tumours other than breast and prostate.
- 3.87 The Committee noted comments received during consultation that, compared with zoledronic acid, denosumab was shown to be more effective and less costly, and therefore in instances in which zoledronic acid was currently used, denosumab may be a more efficient use of NHS resources. The Committee also recognised that denosumab may offer some benefits in terms of administration over intravenous bisphosphonates and have a role in the treatment of people with reduced renal function (see section 3.70). The Committee considered the guideline recommendation for the use of bisphosphonates for pain relief on one hand and the constraints on the appraisal to make recommendations about the use of denosumab for the prevention of skeletal-related events on the other hand. The Committee did not consider that a recommendation about denosumab for the prevention of skeletal-related events would lead to a more efficient use of NHS resources if existing NICE guidance recommended the use of bisphosphonates for pain relief only because the populations, although overlapping, were not necessarily the same. The Committee was not persuaded that the results of the analyses in section 3.55 (which suggested that denosumab may be associated with lower costs than zoledronic acid) should change its decisions that the appropriate comparator for people with bone metastases from prostate cancer was best supportive care and that for this patient group denosumab had not been shown to be a cost-effective use of NHS resources.
- 3.88 The Committee noted comments received at consultation which stated that zoledronic acid was not the only bisphosphonate used in solid tumours other than breast and prostate, and that disodium pamidronate was also used. It discussed whether denosumab should be recommended as an alternative to

disodium pamidronate. The Committee was aware that although zoledronic acid is the only bisphosphonate that has marketing authorisation in this patient group, the data provided by the manufacturer indicated that disodium pamidronate is being prescribed for approximately 20% of the people who are being treated or have been treated with a bisphosphonate (see section 3.39). The Committee took into consideration the price of disodium pamidronate, which is higher than zoledronic acid. It was aware that there is no estimate of clinical effectiveness for denosumab compared with disodium pamidronate in this patient group, but noted the availability of evidence from people with breast cancer (see section 3.13). The Committee concluded that denosumab should also be considered as an alternative where disodium pamidronate was used. In people with bone metastases from solid tumours other than breast and prostate cancers, denosumab was recommended as an alternative option if bisphosphonates would otherwise be prescribed.

3.89 The Committee considered comments received during the consultation on the appraisal consultation document that the fact that denosumab is recommended for the treatment of breast cancer but not for the treatment of prostate cancer could be interpreted as indirect sex discrimination. This is because the vast majority of people with breast cancer are women, and prostate cancer can only occur in biological men. The recommendations therefore mean that people with prostate cancer, that is, men and transgender women, cannot access treatment with denosumab for preventing skeletal-related events. The Committee agreed that the reason denosumab was not recommended for preventing skeletal-related events in prostate cancer was not because prostate cancer occurs in men and transgender women, nor was it related in any way to the different gender profile of the patients. Instead, the Committee considered that the evidence indicates that current clinical management and disease course varies between breast, prostate and other solid tumours. The Committee noted that separate clinical trials have been carried out in these different cancer types, and that the trials showed different efficacy profiles for denosumab between the cancer types. The choice of comparator for denosumab in the different cancer types was informed by its marketing authorisation and the published guidelines. The ICER for using denosumab in prostate cancer compared with best supportive care is high (more than £70,000 per QALY gained and therefore beyond the threshold at which NICE would normally recommend a treatment). The Committee considered that the evidence on different cost-effectiveness profiles for the different types

of disease means that it is doubtful whether the Committee's recommendations can be regarded as treating patients with prostate cancer less favourably than patients with breast cancer. Bearing in mind NICE's duties and functions and the requirement for the Committee's recommendations to be based on the clinical and cost effectiveness of treatments, the Committee considered that the recommendation for prostate cancer was a means of achieving a legitimate aim. Given the high level of the ICER for using denosumab in prostate cancer, the Committee was satisfied that the recommendation is a proportionate means of achieving that aim and that its recommendations do not lead to unlawful discrimination. Therefore, it concluded that it did not need to add to or change its recommendations in light of the consultation comments.

4 Implementation

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has skeletal-related events with bone metastases from solid tumours and the healthcare professional responsible for their care thinks that denosumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal Committee members and NICE project team

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 4 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 David Black

Director of Public Health, Derbyshire County Primary Care Trust

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

Dr Wasim Hanif

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

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

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Anwar Jilani

Technical Lead

Zoe Garrett

Technical Adviser

Lori Farrar

Project Manager

Sources of evidence considered by the Committee

The assessment report for this appraisal was prepared by Aberdeen HTA Group:

- Ford J, Cummins E, Sharma P et al. Systematic review of the clinical and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2011

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). Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Amgen

Professional or specialist and patient or 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

Other consultees:

- Department of Health
- Welsh Government

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

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or 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 were also 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

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

- Amgen

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