- Please note that the Overview was prepared before the errata of the Assessment Report were issued.
- The results of network meta-analysis and the cost-effectiveness modelling by the Assessment Group reported in this document have been changed.
- These results should be read in conjunction with the Erratum of the Assessment Report.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

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

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- The use of bisphosphonates and best supportive care in clinical practice varies:
  - For which tumour types and patients are bisphosphonates and/or best supportive care used?
  - Which bisphosphonates are most commonly used?
  - Where may denosumab be used in clinical practice?
- Denosumab is administered as a subcutaneous injection, whereas bisphosphonates are often administered by intravenous infusion. Does the Committee consider there to be benefits in methods of administration?
- The denosumab clinical trials recruited a small number of patients from the UK. Does the Committee consider that the trial population is generalisable to the population in England and Wales?
- The primary end-point in the denosumab clinical trials is a composite outcome: skeletal-related events. This outcome includes both complications of bone metastases, some of which may be asymptomatic, as well as therapeutic or preventive treatments. Does the Committee

consider the outcomes and data collected in the clinical trial to be appropriate and the differences meaningful?

- The clinical trials collected data for skeletal-related events, pain and analgesic use, and health-related quality of life. Has denosumab demonstrated efficacy in these outcomes across the range of tumour types and in patients with different skeletal-related event histories?
- The head-to-head evidence compares denosumab and zoledronic acid. For the comparison of denosumab with other comparators and best supportive care, a network meta-analysis was performed. Does the Committee consider there are sufficient data to inform conclusions on the effectiveness of denosumab compared with these comparators?
- People with reduced renal function may be unable to receive bisphosphonates, or have trouble tolerating them. Denosumab may be used in people regardless of their renal function. Does the Committee consider that people with poor renal function are a separate subgroup?

Cost effectiveness

- Both the Assessment Group and manufacturer analyses suggest that denosumab is associated with a small gain in incremental quality-adjusted life years (QALYs). The incremental cost-effectiveness ratios (ICERs) are sensitive to assumptions about costs (such as drug, administration and resource costs). Are the cost and resource assumptions used in the economic modelling considered appropriate?
- The Assessment Group presents a separate subgroup for non-small cell lung cancer (NSCLC). The manufacturer submission indicates that the clinical trial was not powered to detect differences in this group. Should NSCLC be considered separately from the other solid tumours data?
- In the Assessment Group analysis, the cost-effectiveness results are presented for all patients, and separately for those with a prior skeletal-related event and those without a prior skeletal-related event. Is it appropriate to consider the separate estimates of cost effectiveness for patients with or without a prior skeletal-related event?
- Where analyses are comparable, the overall findings of the manufacturer and Assessment Group models are generally consistent for breast and

prostate cancer with some differences between models in the results for other solid tumours. Does the Committee consider that denosumab has been shown to be cost effective:

  - In comparison with bisphosphonates and best supportive care?
  - For all solid tumours or subgroups of these?
  - For patients regardless of skeletal related event history?

- The Assessment Group suggests that the cost effectiveness of denosumab in comparison with best supportive care may be over estimated because the model assumes the rates of adverse events for best supportive care are zero. How does this factor influence decision making?

1 Background: Clinical need and practice

1.1 Bone is one 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.

1.2 Bone metastases affect the balance of activity between osteoclasts (cells that resorb bone) and osteoblasts (bone-forming cells). This results in a locally increased rate of remodelling and the development of bone lesions. The presence of bone metastases is associated with a worse prognosis, reduced quality of life and increased risk of complications from bone weakness or disrupted calcium homoeostasis. The complications include pathological fractures (defined as pathological because minimal or no force is required), spinal cord compression, radiation to the bone or surgery to the bone: 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 patients with bone metastases often report inadequate pain relief with analgesics.

1.3 The manufacturer estimated that there are over 150,000 patients in the UK with solid tumours and bone metastases, of which breast and prostate cancer account for more than 80%. Approximately 0.5% of women with breast cancer have bone metastases at diagnosis and 4.7% develop bone metastases in 5 years. In women with breast cancer, bone metastases are associated with reduced median survival of approximately 2 years. The manufacturer's submission reports that 11% of patients with prostate cancer present with bone metastases at initial staging. No estimates for the proportion of patients with recurrent disease and subsequent metastases are available. In men with prostate cancer the presence of bone metastases reduces 5-year survival from 56% to 3%.

1.4 The primary aim of treatment of bone metastases is to manage skeletal morbidity by delaying or preventing skeletal-related events. A second aim is to delay the development of pain and reduce its severity. Current management of bone metastases and its complications include radiotherapy, orthopaedic surgery, bone-targeting radio-pharmaceuticals and chemotherapy. Bisphosphonates reduce bone resorption by inhibiting osteoclasts and are used to prevent or delay skeletal complications associated with bone metastases. Four bisphosphonates are currently licensed for the management of bone metastases or the prevention of skeletal-related events in patients with solid tumours. These are zoledronic acid, disodium pamidronate, sodium clodronate and ibandronic acid. Zoledronic acid is most frequently used and is the only bisphosphonate that is licensed for the prevention of skeletal-related events in advanced malignancies involving bone without specifying the primary tumour type. Disodium pamidronate and sodium clodronate are licensed in breast cancer and multiple myeloma, and ibandronic acid is licensed in breast cancer only.

1.5 Management of bone metastases varies between each primary cancer type. 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81) recommends offering bisphosphonates to patients with newly diagnosed breast cancer and bone metastases to prevent skeletal-related events and reduce pain. 'Prostate cancer: diagnosis and treatment' (NICE clinical guideline 58) recommends bisphosphonates in men with hormone-refractory prostate cancer to prevent bone metastases only when other treatments such as analgesics and palliative radiotherapy have failed. In patients with lung cancer with bone metastases that need palliation and for whom standard analgesic treatments are inadequate, single-fraction radiotherapy is recommended ('Lung cancer: the diagnosis and treatment of lung cancer', NICE clinical guideline 121). 'Metastatic spinal cord compression: diagnosis and management of adults at risk of and with metastatic spinal cord compression' (NICE clinical guideline 75) recommends bisphosphonates in patients with breast cancer or multiple myeloma with vertebral involvement to reduce pain and the risk of vertebral fracture/collapse. In patients with vertebral involvement from prostate cancer bisphosphonates are recommended only if conventional analgesia fails to control pain. The Assessment report indicates no clear UK guidelines for the use of bisphosphonates for bone metastases in tumour types other than breast and prostate.

2 The technology

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 is licensed 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 administered 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 one 120 mg vial is £309.86 (excluding VAT; BNF 62). A year of treatment (13 doses) would cost £4028.18 (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. The patient access scheme is a simple discount of [redacted] on the list price of denosumab, which would result in an NHS acquisition price of [redacted] per 120 mg vial and the cost of a year of treatment of [redacted] The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of denosumab within its licensed indication for the treatment of bone metastases from solid tumours and multiple myeloma.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	Adults with bone metastases from solid tumours and adults with multiple myeloma	The population has been divided into subgroups of breast, prostate, NSCLC and other solid tumours Multiple myeloma is not included in the marketing authorisation and was removed from the decision problem

The population in the manufacturer's submission was 'adults with bone metastases from solid tumours' to be similar to the approved licence. The manufacturer presented data separately for patients with breast cancer, prostate cancer and other solid tumours, as well as an integrated analysis across all solid tumours. A subgroup of NSCLC was not presented separately because the trial was not powered to detect differences in outcomes.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Intervention	Denosumab	None
Comparators	Bisphosphonates such as sodium clodronate, disodium pamidronate, ibandronic acid and zoledronic acid Best supportive care	In breast cancer, denosumab is compared with bisphosphonates (zoledronic acid, disodium pamidronate, ibandronic acid and sodium clodronate) In prostate cancer, NSCLC and other solid tumours, denosumab is compared with zoledronic acid and best supportive care

In the manufacturer's submission, zoledronic acid was considered the primary comparator for breast cancer, and disodium pamidronate and ibandronic acid supplementary comparators. For prostate cancer and other solid tumours, if patients had no pain or no prior skeletal-related event, best supportive care was considered the comparator, but if patients had pain and a prior skeletal-related event zoledronic acid was considered the comparator. Disodium pamidronate was included as a supplementary comparator for other solid tumours because, although it is not licensed for this indication, UK data suggested it was in use in clinical practice. Sodium clodronate was not included as a comparator in the manufacturer's submission because data

collected from the IMS oncology analyser suggested UK usage to be less than 5%.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Outcomes	Time to first skeletal event Time to first and subsequent skeletal-related event Incidence of skeletal-related events (pathological fracture, spinal cord compression, radiation or surgery to the bone) Skeletal morbidity rate Hypercalcaemia Survival Pain Health-related quality of life Adverse effects of treatment	If evidence allows, each type of skeletal-related event is presented separately

In the manufacturer's submission the distribution of skeletal-related events was presented separately for each study and in the integrated analysis across all solid tumour types.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective	None

Other considerations	Data for each type of skeletal-related event should be presented separately in the submission The appraisal should consider patient groups based on location or type of primary cancer including variations in current standard management for these groups If evidence allows, a subgroup based on prior history of skeletal-related events should be considered Guidance will only be issued in accordance with the marketing authorisation	See comments above If evidence allowed, subgroups based on prior history of skeletal-related event are considered

In the manufacturer's submission, data by prior skeletal-related event history are presented separately for each study and for the integrated analysis across all solid tumour types.

3.2 For breast cancer the Assessment Group compares denosumab as an alternative to bisphosphonates for patients with bone metastases (that is, as a first-line treatment), and in the economic analysis as an alternative to best supportive care in patients with bone metastases not able to have bisphosphonates. The manufacturer's submission includes the former analysis only. For prostate cancer and other solid tumours, both the Assessment Group and the manufacturer compare denosumab as an alternative to best supportive care (that is, as a first-line treatment) and as an alternative to bisphosphonates (that is, as a second-line treatment). The manufacturer defines the group for whom bisphosphonates is the comparator as patients with bone metastases with pain and a prior skeletal-related event and the group for whom best supportive care is the comparator as patients with bone metastases with no pain or no prior skeletal-related event.

4 Clinical-effectiveness evidence

4.1 The Assessment Group identified three denosumab studies. One of these studies was in patients with breast cancer, one in patients

with prostate cancer and one in patients with solid tumours (excluding breast and prostate) or multiple myeloma. All of the studies compared denosumab with zoledronic acid. The outcomes reported in these studies included time to first on-study skeletal-related event, risk of first and subsequent on-study skeletal-related event, skeletal morbidity rate (defined as the ratio of the number of skeletal-related events per patient divided by the patient's time at risk), incidence of skeletal-related events, proportion of hypercalcaemia, overall survival rate, pain measured using the Brief Pain Inventory-Short Form (BPI-SF), health-related quality of life measured using both the Functional Assessment of Cancer Therapy and the EQ-5D and adverse events related to treatment. The studies were powered to detect non-inferiority and superiority to zoledronic acid with respect to time to first on-study skeletal-related event and superiority to zoledronic acid with respect to risk of first and subsequent on study skeletal-related events.

4.2 Because there were no direct comparisons of denosumab with bisphosphonates other than zoledronic acid, or best supportive care, the Assessment Group also undertook a network meta-analysis. The Assessment Group identified 39 studies which met the inclusion criteria for the review. However, 31 studies were excluded because they did not report uniform definitions of skeletal-related events, standardised skeletal-related event rates or separate outcomes for different cancer types. Eight studies (including the three denosumab studies) were included in the network meta-analysis – 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 included subgroups of patients with NSCLC and other solid tumours excluding NSCLC, so the Assessment Group considered these two subgroups separately in their analysis. Of these subgroups the overview only describes the NSCLC analysis.

4.3 For patients with bone metastases from breast cancer, evidence was available for the network meta-analysis to link denosumab, zoledronic acid, pamidronate and placebo. For patients with bone metastases from prostate cancer, NSCLC and other solid tumours, evidence was available for the network meta-analysis to link denosumab, zoledronic acid and placebo. Outcomes in the network meta-analysis were time to first skeletal-related event and risk of first and subsequent skeletal-related event. If data were available, skeletal morbidity rate ratios and the proportion of patients with at least one on-study skeletal-related event were also analysed.

Breast cancer

4.4 One randomised double-blind study was identified by the Assessment Group that compared denosumab with zoledronic acid in patients with breast cancer (Stopeck 2010). This study also formed part of the manufacturer's submission.

4.5 The Stopeck study enrolled people (n = 2046) with confirmed breast cancer and at least one bone metastasis from 322 centres in Europe, North America, South America, Japan, Australia, India and South Africa. [redacted] of patients were from the UK. Patients received 120 mg denosumab subcutaneously and placebo intravenously or 4 mg zoledronic acid intravenously and placebo subcutaneously every 4 weeks. Follow-up was for approximately 34 months. The discontinuation rate (excluding death and disease progression) was [redacted] in the denosumab group and [redacted] the zoledronic acid group.

Breast cancer: primary outcome

4.6 The median time to first skeletal-related event was not reached in the denosumab group compared with 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). Denosumab achieved both non-inferiority and superiority for time to first skeletal-related event. In

patients with a first on-study skeletal-related event, the most commonly occurring skeletal-related events were pathological fracture (67% of the denosumab group and 64% of the zoledronic acid group) and radiation to bone (26% of the denosumab group and 32% of the zoledronic acid group). For patients with a prior skeletal-related event, denosumab statistically significantly delayed time to first on-study skeletal-related event compared with zoledronic acid [redacted]. For patients without a prior skeletal-related event there was a non-statistically significant difference in favour of denosumab compared with zoledronic acid [redacted].

Breast cancer: secondary outcomes

4.7 Risk of first and subsequent skeletal-related event 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). The most commonly occurring skeletal-related events were pathological fracture (65.2% of the denosumab group and 63.8% of the zoledronic acid group) and radiation to bone (27.2% of the denosumab group and 31.1% of the zoledronic acid group). For both patients with and without a prior history of skeletal-related event, the risk of first and subsequent skeletal-related event was reduced by denosumab compared with zoledronic acid ([redacted]. Skeletal morbidity rate and annualised skeletal-related event rate are shown in table 1.

4.8 There was no significant difference in median overall survival for the denosumab group ([redacted]) compared with the zoledronic group acid ([redacted]; HR 0.95, 0.81 to 1.11, p = 0.49).

4.9 The proportion of patients with no or mild pain reporting moderate or severe pain in each study visit week was lower in the denosumab group (range 14.8% to 19.9%) compared with the

zoledronic acid group (range 22.1% to 27.4%). The median time to developing moderate or severe pain in patients with no or mild pain at baseline was reported to be significantly longer in the denosumab group compared with the zoledronic acid group (295 compared with 176 days; HR 0.78, 95% CI 0.67 to 0.92, p = 0.0024). There was [redacted] in time to pain improvement (≥ 2 point decrease from baseline) [redacted] There was [redacted] at study end-point in the use of strong analgesics. At [redacted] time points, there was a statistically significant [redacted] of patients who needed strong analgesics in the [redacted].

Breast cancer: health-related quality of life

4.10 There was [redacted]. For both components of EQ-5D (the health index and the visual analogue scale (VAS), there was [redacted] between denosumab and zoledronic acid for average AUC for both EQ-5D health index and VAS score [redacted] Both the denosumab and zoledronic acid groups [redacted] in the mean EQ-5D health state index at most study visits.

Breast cancer: adverse events

4.11 The incidence of serious adverse events and adverse events leading to discontinuation were similar in the denosumab and zoledronic acid groups (44% compared with 47% and 10% compared with 12% respectively). There was a higher incidence of hypocalcaemia events in the denosumab group than in the

zoledronic acid group (5.5% compared with 3.4% respectively). [redacted] of hypercalcaemia were reported in the denosumab group compared with [redacted] in the denosumab group. The rate of osteonecrosis of the jaw was similar between the denosumab group and the zoledronic acid group (2.0% compared with 1.4%). 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%).

Table 1 Key outcome data: breast cancer

	Denosumab (n = 1026)	**Zoledronic acid (n = 1020)**	**Values**
Time to first skeletal-related event (median months)	Not reached	26.4	HR 0.82, 95% CI 0.71 to 0.95 p < 0.0001 (non-inferiority) p = 0.01 (superiority)
With prior history of skeletal-related event			[redacted]
Without prior history of skeletal-related event			[redacted]
Risk of first and subsequent skeletal-related event			[redacted]
With prior history of skeletal-related event			[redacted]
Without prior history of skeletal-related event			[redacted]
Skeletal morbidity rate (mean, events per patient per year)	0.45	0.58	p = 0.004
Annualised skeletal-related event rate (with 21-day window)*	[redacted]	[redacted]	
Hypercalcaemia	[redacted]	[redacted]	
Overall survival (median months)	[redacted]	[redacted]	HR 0.95, 95% CI 0.81 to 1.11, p = 0.4921

Time to developing moderate or severe pain in patients with no or mild pain at baseline (median days)	[redacted]	[redacted]	[redacted]

CI, confidence interval; HR, hazard ratio; RR, relative risk, * subsequent events must have occurred at least 21 days apart from the most recent event to ensure that linked events (for example, surgery to repair a fracture or multiple doses of radiation during a course of treatment) were not counted as separate skeletal-related events

Breast cancer: network meta-analysis

4.12 Four randomised controlled trials in patients with breast cancer were identified by the Assessment Group. These four studies were:

- denosumab compared with zoledronic acid (Stopeck 2010)
- zoledronic acid compared with pamidronate (Rosen 2003a)
- zoledronic acid compared with placebo (Kohno 2005)
- pamidronate compared with placebo (Lipton 2000).

The results of the network meta-analysis are presented in table 2. Denosumab statistically significantly reduced time to first skeletal-related event and first and subsequent skeletal-related event compared with zoledronic acid, pamidronate and placebo. Denosumab also statistically significantly reduced the skeletal morbidity rate compared with placebo. Other comparisons with denosumab were not statistically significant.

Table 2 Results of Assessment Group network meta-analysis: breast cancer

Comparison	Denosumab compared with zoledronic acid	Denosumab compared with pamidronate	Denosumab compared with placebo	Zoledronic acid compared with placebo
Time to first on-study skeletal-related event HR (95% CI)	0.81 (0.78 to 0.83)	0.89 (0.86 to 0.93)	0.48 (0.46 to 0.51)	0.57 (0.55 to 0.59)
Risk of first and subsequent skeletal-related event RR (95% CI)	0.75 (0.73 to 0.76)	0.57 (0.55 to 0.59)	0.42 (0.41 to 0.43)	0.55 (0.54 to 0.56)
Skeletal morbidity rate RR (95% CI)	0.90 (0.67 to 1.09)	0.73 (0.41 to 1.06)	0.47 (0.25 to 0.67)	0.52 (0.32 to 0.70)
Any skeletal-related event OR (95% CI)	0.77 (0.11 to 4.86)	Not performed	0.36 (0.03 to 3.96)	0.47 (0.09 to 2.23)
CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk				

Breast cancer: summary of clinical effectiveness

4.13 Direct head-to-head evidence reported a statistically significant difference in favour of denosumab compared with zoledronic acid for both the time to first on-study skeletal-related event and the risk of developing first and subsequent on-study skeletal-related events. Skeletal morbidity rate was significantly lower in the denosumab group compared with the zoledronic acid group. There were no differences in overall survival for the denosumab group compared with the zoledronic acid group. The proportion of patients with no or mild pain who reported moderate or severe pain was lower in the denosumab group compared with the zoledronic acid group. The results from the network meta-analysis showed that denosumab compared with zoledronic acid, placebo or pamidronate significantly delayed the time to first skeletal-related event and significantly reduced the risk of first and subsequent skeletal-related event, and that denosumab compared with placebo significantly reduced the skeletal morbidity rate.

Prostate cancer

4.14 One double-blind, multicentre, randomised, controlled study was identified by the Assessment Group that compared denosumab with zoledronic acid in patients with prostate cancer (Fizazi 2011). This study also formed part of the manufacturer's submission.

4.15 The study by Fizazi enrolled men (n = 1901) aged 18 years or older with confirmed prostate cancer and at least one bone metastasis, from 342 centres in 39 countries. The proportion of patients from the UK was [redacted]. Patients received a subcutaneous injection of 120 mg denosumab and an intravenous infusion of placebo or an intravenous infusion of 4 mg zoledronic acid and a subcutaneous injection of placebo every 4 weeks. Follow-up was 41 months for the blinded treatment phase. The discontinuation rate (excluding death and disease progression) was [redacted] in the denosumab group and [redacted] the zoledronic acid group.

Prostate cancer: primary outcome

4.16 Denosumab statistically significantly delayed the median time to first on-study skeletal-related event compared with zoledronic acid (20.7 compared with 17.1 months, HR 0.82, 95% CI 0.71 to 0.95, p = 0.008 superiority). Denosumab achieved non-superiority and superiority for time to first skeletal-related event. The most commonly occurring skeletal-related events were radiation to bone (51.9% denosumab and 52.6% zoledronic acid) and pathological fracture (40.2% denosumab and 37.1% zoledronic acid). For patients with no prior skeletal-related event, denosumab statistically significantly delayed time to first on-study skeletal-related event compared with zoledronic acid (HR 0.80, 95% CI 0.67 to 0.95, p = 0.011). For patients with a prior skeletal-related event [redacted].

Prostate cancer: secondary outcomes

4.17 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 superiority). The most commonly occurring skeletal-related events were radiation to bone (53.4% denosumab and 56.5% zoledronic acid) and pathological fracture (38.1% denosumab and 34.8% zoledronic acid). For patients with no prior skeletal-related event, [redacted] while for those with a prior skeletal-related event [redacted] Outcomes reports for skeletal morbidity rate and annualised skeletal-related event rate are presented in table 3.

4.18 Median overall survival was similar between 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).

4.19 Denosumab delayed the time to development of moderate or severe pain in patients with no or mild pain at baseline by 1 month compared with 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). Denosumab statistically significantly decreased the proportion of patients with no or mild pain at baseline who progressed to moderate or severe pain (relative decrease of [redacted] over 73 weeks). The median time to worsening pain (≥ 2-point increase from baseline in BPI-SF worst pain score) was comparable between denosumab and zoledronic acid ([redacted] compared with [redacted] months, [redacted]). There was no significant difference in time to pain improvement (≥ 2-point decrease from baseline) between denosumab and zoledronic acid. There were no statistically significant differences in the use of strong analgesics.

Prostate cancer: health-related quality of life

4.20 [redacted]between the FACT-G AUC score or FACT-P AUC score when denosumab was compared with zoledronic acid [redacted]A comparison between treatment groups showed [redacted]in the FACT-G total score in the denosumab group compared with the zoledronic acid group[redacted]

Prostate cancer: adverse events

4.21 The incidence of serious adverse events and adverse events leading to discontinuation were similar in the denosumab and zoledronic acid groups (63% versus 60% and 17% versus 15% respectively). There were more hypocalcaemia adverse events in the denosumab group compared with the zoledronic acid group (13% [121/943] compared with 6% [55/945] respectively). In the denosumab group, [redacted] of patients experienced hypercalcaemia compared with [redacted] in the zoledronic acid group. 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 compared with the zoledronic acid group (15% compared with 16% respectively. During the first 3 days of treatment, fewer patients experienced symptoms associated with acute phase reactions in the denosumab group (8%) compared with the zoledronic acid group (18%).

Table 3 Key outcome data: prostate cancer

	Denosumab (n = 950)	Zoledronic acid (n = 951)	Values
Time to first skeletal-related event (median months)	20.7	17.1	HR 0.82, 95% CI 0.71 to 0.95 p = 0.0002 (non-inferiority) p = 0.008 (superiority) [redacted]
With prior history of skeletal-related event			p = 0.3657 HR 0.80, 95% CI 0.67 to 0.95, p = 0.011
Without prior history of skeletal-related event			
Risk of first and subsequent skeletal-related event			[redacted] p = 0.008 (superiority)
With prior history of skeletal-related event			[redacted]
Without prior history of skeletal-related event			[redacted]
Skeletal morbidity rate (mean, events per patient per year)	[redacted]	[redacted]	[redacted]
Annualised skeletal-related event rate (with 21-day window)*	[redacted]	[redacted]	
Hypercalcaemia	[redacted]	[redacted]	
Overall survival, median months	19.4	19.8	HR 1.03, 95% CI 0.91 to1.17, p = 0.6511
Time to developing moderate or severe pain in patients with no or mild pain at baseline (median months)	5.8	4.9	HR 0.89, 95% CI 0.77 to 1.04, p = 0.1416
CI, confidence interval; HR, hazard ratio; RR, relative risk, * subsequent events must have occurred at least 21 days apart from the most recent event to ensure that linked events (for example, surgery to repair a fracture or multiple doses of radiation during a course of treatment) were not counted as separate skeletal-related events			

Prostate cancer: network meta-analysis

4.22 Two randomised controlled trials in patients with prostate cancer were identified by the Assessment Group as meeting the criteria for inclusion in the network meta-analysis. The two studies were denosumab compared with zoledronic acid (Fizazi 2011) and zoledronic acid compared with placebo (Saad 2002). The results of the network meta-analysis are presented in table 4. The analysis showed that denosumab statistically significantly delayed time to first skeletal-related event and reduced the risk of developing first and subsequent skeletal-related events compared with zoledronic acid or placebo. For skeletal morbidity rate there was a statistically significant difference in favour of denosumab compared with placebo. Other comparisons with denosumab were not statistically significant.

Table 4 Results of Assessment Group network meta-analysis: prostate cancer

Comparison	Denosumab compared with zoledronic acid	Denosumab compared with placebo	Zoledronic acid compared with placebo
Time to first on-study skeletal-related event HR (95% CI)	0.57 (0.54 to 0.59)	0.45 (0.43 to 0.48)	0.66 (0.64 to 0.68)
Risk of first and subsequent skeletal-related event RR (95% CI)	0.83 (0.81 to 0.85)	0.56 (0.54 to 0.58)	0.69 (0.67 to 0.71)
Skeletal morbidity rate RR (95% CI)	0.95 (0.46 to 1.47)	0.52 (0.07 to 0.82)	0.54 (0.11 to 0.83)
Any skeletal-related event OR (95% CI)	0.81 (0.07 to 10.40)	0.53 (0.01 to 18.80)	0.64 (0.05 to 7.51)
CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk			

Prostate cancer: summary of clinical effectiveness

4.23 Direct head-to-head evidence reported a statistically significant difference in favour of denosumab compared with zoledronic acid in

both the median time to first on-study skeletal-related event and the risk of developing first and subsequent on-study skeletal-related events. The annual skeletal morbidity rate was also significantly lower in the denosumab group, as was the annualised skeletal-related event rate. Median overall survival was similar between the denosumab group and the zoledronic acid group. The network meta-analysis reported statistically significant differences in favour of denosumab compared with zoledronic acid for time to first on-study skeletal-related event and risk of developing first and subsequent skeletal-related events.

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

4.24 One randomised double-blind study was identified by the Assessment Group that compared denosumab with zoledronic acid in patients with bone metastases secondary to other solid tumours or multiple myeloma (Henry 2011). The Henry study formed part of the manufacturer's submission.

4.25 The study by Henry enrolled patients (N=1776) aged 18 years or older with confirmed solid tumours (except breast and prostate) or multiple myeloma and at least one bone metastasis or osteolytic lesion (in the case of multiple myeloma), from 321 centres worldwide. Overall 0.6% of patients were from the UK. Patients received 120 mg denosumab subcutaneously (plus intravenous placebo) or 4 mg zoledronic acid intravenously (adjusted for renal impairment plus subcutaneous placebo) every 4 weeks. Before the randomisation process, patients were stratified by tumour type that included NSCLC, myeloma or 'other'. In the study 40% of patients had NSCLC, 10% had multiple myeloma and 50% had other tumours. A post-hoc analysis of other solid tumours excluding multiple myeloma (N=1597) was reported in the manufacturer's submission and will be summarised below. Length of follow-up in the study was 34 months. The discontinuation rate (excluding death

and disease progression) was [redacted] in the denosumab group and [redacted] the zoledronic acid group.

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

4.26 The median time to first on-study skeletal-related event was longer for denosumab ([redacted]) than zoledronic acid ([redacted]). Denosumab achieved both inferiority and superiority for time to first skeletal-related event. The most commonly occurring skeletal-related events were radiation to bone (47% denosumab and 49.5% zoledronic acid) and pathological fracture (39% denosumab and 37.2% zoledronic acid). For those patients with no prior skeletal-related event, time to first on-study skeletal-related event was [redacted] while for those with a prior skeletal-related event [redacted].

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

4.27 Denosumab reduced the risk of developing first and subsequent skeletal-related events compared with zoledronic acid ([redacted]). The most commonly occurring skeletal-related events were [redacted] For patients with no prior skeletal-related event, the risk of first and subsequent on-study skeletal-related events was [redacted] while for those with a prior skeletal-related event [redacted]

Skeletal morbidity rate and annualised rate of skeletal-related event are presented in table 5.

4.28 No difference in median overall survival was observed between the denosumab group [redacted] and the zoledronic acid group [redacted]

4.29 The median time to developing moderate or severe worst pain was evaluated in a subgroup of patients with no or mild pain at baseline. The median time to developing moderate or severe worst pain (worst pain score > 4) in this group was longer in the denosumab group ([redacted]) than in the zoledronic acid group ([redacted]). There was no statistically significant difference at study end-point in the use of strong analgesics. At [redacted] time points, a [redacted] of patients required strong analgesics in the zoledronic acid group.

Other solid tumours (including non-small cell lung cancer): health-related quality of life

4.30 The FACT-G total mean change score from baseline to week 45 was [redacted]. Data for EQ-5D were taken from the clinical study report and include patients with multiple myeloma. A [redacted] mean change in EQ-5D health index score and VAS score was reported from baseline to the weekly visit through to week 45 for denosumab and zoledronic acid. There was [redacted] between denosumab and zoledronic acid in the EQ-5D AUC for health index or VAS [redacted].

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

4.31 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 compared with 5.8% of patients in the zoledronic acid group. There was a higher incidence of hypercalcaemia in the denosumab group ([redacted] compared with the zoledronic acid group ([redacted] 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%) compared to 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%).

Table 5 Key outcome data: other solid tumours (including non-small cell lung cancer)

	Denosumab (n = 800)	Zoledronic acid (n = 797)	Values
Time to first skeletal-related event (median months)	[redacted]	[redacted]	[redacted] p = 0.03 (superiority) p = 0.001 (non-inferiority)
With prior history of skeletal-related event			[redacted]
Without prior history of skeletal-related event			[redacted]
Risk of first and subsequent skeletal-related event			[redacted] (superiority)
With prior history of skeletal-related event			[redacted]
Without prior history of skeletal-related event			[redacted]
Skeletal morbidity rate (mean, events per patient per year)	[redacted]	[redacted]	
Annualised skeletal-related event rate (with 21-day window)*	[redacted]	[redacted]	
Hypercalcaemia**	[redacted]	[redacted]	
Overall survival, median months	[redacted]	[redacted]	[redacted]
Time to developing moderate or severe pain in patients with no or mild pain at	[redacted]	[redacted]	[redacted]

baseline (median months)
CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; RR, relative risk, * subsequent events must have occurred at least 21 days apart from the most recent event to ensure that linked events (for example, surgery to repair a fracture or multiple doses of radiation during a course of treatment) were not counted as separate skeletal-related events, ** grade 3 and 4 hypocalcaemia

Other solid tumours (including non-small cell lung cancer): network meta-analysis

4.32 Two studies in patients with other solid tumours excluding breast cancer and prostate cancer but including NSCLC were identified by the Assessment Group. The two studies were denosumab compared with zoledronic acid (Henry 2011) and zoledronic acid compared with placebo (Rosen 2003b). The Assessment Group noted that including a mixture of cancers in a network meta-analysis increases heterogeneity and so the results should be interpreted with caution. The results of the network meta-analysis are presented in table 6. There was a statistically significant difference in time to first on-study skeletal-related event and the risk of first and subsequent on-study skeletal-related event for denosumab compared with zoledronic acid or placebo. Other comparisons of denosumab were not statistically significant.

Table 6 Results of Assessment Group network meta-analysis: other solid tumours (including non-small cell lung cancer)

Comparison	Denosumab compared with zoledronic acid	Denosumab compared with placebo	Zoledronic acid compared with placebo
Time to first on-study skeletal-related event HR (95% CI)	0.93 (0.90 to 0.96)	0.44 (0.42 to 0.46)	0.53 (0.51 to 0.54)
Risk of first and subsequent skeletal-related event RR (95% CI)	0.87 (0.85 to 0.89)	0.63 (0.61 to 0.66)	0.75 (0.74 to 0.77)
Proportion of patients with on-study skeletal-related event OR (95% CI)	0.79 (0.07 to 9.45)	0.58 (0.02 to 19.48)	0.74 (0.06 to 8.83)
CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; OR, odds ratio; RR, relative risk			

Other solid tumours (including non-small cell lung cancer): summary of clinical effectiveness

4.33 Direct head-to-head evidence reported that denosumab delayed time to first on-study skeletal-related event compared with zoledronic acid in patients with bone metastases from other solid tumours. A significant difference was reported in the risk of developing first and subsequent on-study skeletal-related events. The skeletal morbidity rate and annualised skeletal-related event rate were also significantly lower in the denosumab group. The network meta-analysis reported a statistically significant difference in favour of denosumab compared with zoledronic acid for time to first on-study skeletal-related event and risk of developing first and subsequent on-study skeletal-related events. A key limitation of the network meta-analysis was the small number of trials included, which adds to the uncertainty in the results.

Non-small cell lung cancer

4.34 One randomised double-blind study was identified by the Assessment Group that compared denosumab with zoledronic acid in patients with bone metastases secondary to other solid tumours including NSCLC (Henry 2011). This was the same study described in the section for other solid tumours.

Non-small cell lung cancer: key outcomes

4.35 Denosumab delayed the time to first on-study skeletal-related event compared with zoledronic acid (HR 0.84, 95% CI 0.64 to 1.10, p = 0.20). The median time to first on-study skeletal-related event was [redacted] The risk of developing first and subsequent skeletal-related events was [redacted] The mean number of skeletal-related events per patient was [redacted] An ad hoc analysis (as outlined in Henry 2011) for overall survival reported that denosumab significantly improved overall survival relative to zoledronic acid by 21% (HR 0.79, 95% CI 0.65 to 0.95). Skeletal morbidity rate, pain and health-related quality of life were not reported for the NSCLC group. There were no adverse event data for the NSCLC subgroup.

Non-small cell lung cancer: network meta-analysis

4.36 Two randomised controlled trials in patients with other solid tumours (excluding breast cancer and prostate cancer) were identified by the Assessment Group as meeting the criteria for inclusion in the network meta-analysis (see other solid tumours section for further details). Both these trials enabled a subgroup analysis of NSCLC. The results of the network meta-analysis are presented in table 7. The results showed that denosumab

compared with zoledronic acid or placebo statistically significantly delayed time to first on-study skeletal-related event. Denosumab reduced the risk of first and subsequent skeletal-related events compared with zoledronic acid or placebo, although only the comparison with placebo was statistically significant. For the proportion of patients with an on-study skeletal-related event the differences were not statistically significant. These results should be interpreted with additional caution because this outcome does not differentiate between length of study.

Table 7 Results of Assessment Group network meta-analysis: non-small cell lung cancer

Comparison	Denosumab compared with zoledronic acid	Denosumab compared with placebo	Zoledronic acid compared with placebo
Time to first on-study skeletal-related event HR (95% CI)	0.79 (0.76 to 0.81)	0.66 (0.63 to 0.68)	0.86 (0.84 to 0.89)
Risk of first and subsequent skeletal-related event RR (95% CI)	0.97 (0.95 to 1.01)	0.69 (0.66 to 0.73)	0.73 (0.71 to 0.75)
Proportion of patients with on-study skeletal-related event OR (95% CI)	0.96 (0.08 to 11.7)	0.83 (0.02 to 30.6)	0.87 (0.07 to 11.2)

CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; OR, odds ratio; RR, relative risk

Non-small cell lung cancer: summary of clinical effectiveness

4.37 Direct head-to-head evidence showed that for patients with bone metastases from NSCLC there was a non-significant difference favouring denosumab over zoledronic acid in time to first on-study skeletal-related event. The risk of developing first and subsequent skeletal-related events was [redacted] denosumab and zoledronic acid groups. The results of the network meta-analysis showed that denosumab compared with zoledronic

acid or placebo statistically significantly delayed time to first on-study skeletal-related event. Denosumab reduced the risk of first and subsequent skeletal-related events compared with zoledronic acid or placebo, but this difference was only statistically significant in the comparison with placebo. Fewer outcomes were available from the studies in NSCLC than were reported for breast cancer, prostate cancer or other solid tumours and so the data are limited.

5 Comments from other consultees

5.1 The experts noted that in patients with metastatic breast cancer, prostate cancer or other solid tumours, bone is one of the most common sites for the cancer to spread to. These patients are at a high risk of developing skeletal-related events, which can greatly affect quality of life causing disability, pain and hospitalisation. They noted that maintaining a good quality of life is important to patients with metastatic cancer. The primary goal for the treatment of bone metastases is to prevent skeletal-related events. The current treatment for bone metastases and the prevention of skeletal-related events are the bisphosphonates, such as zoledronic acid, which is administered by intravenous injection every 3 to 4 weeks.

5.2 The experts noted that studies comparing denosumab with zoledronic acid showed that denosumab was superior to zoledronic acid in delaying the first on-study skeletal-related event and the time to multiple on-study skeletal-related events. Denosumab has also been shown to delay the worsening of pain in patients with advanced cancer and bone metastases.

5.3 The experts noted that denosumab may be able to offer advantages over zoledronic acid because it is administered subcutaneously rather than intravenously. The subcutaneous injection could be given in the community rather than in hospital, saving the patient the added financial costs of travelling to a

hospital, increasing convenience for them, and reducing costs in the acute sector. Another advantage of denosumab is that it does not require renal function monitoring, unlike zoledronic acid, and so it could be an additional treatment option for patients with renal failure or renal insufficiency for whom zoledronic acid is not suitable. In addition, denosumab causes relatively fewer acute phase reactions compared with zoledronic acid.

6 Cost-effectiveness evidence

Published literature

6.1 The manufacturer's literature review identified 21 studies that contained economic analyses. All were 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, most were in breast cancer (eight studies), two in prostate cancer, one in lung cancer and one in renal carcinoma. The Assessment Group identified 11 studies, one of which included denosumab. This study was in patients with prostate cancer and denosumab was compared with zoledronic acid. The study used US cost data and reported outcomes as costs per skeletal-related event avoided.

Manufacturer's submission

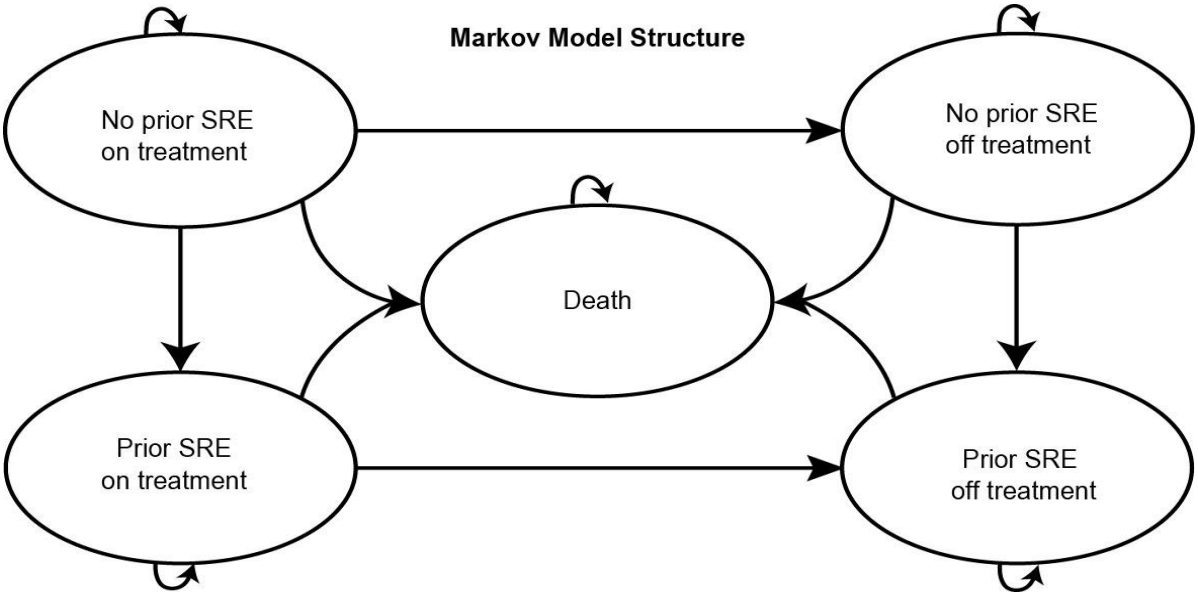
6.2 The manufacturer of denosumab has submitted a Markov economic model. The model compares the cost effectiveness of denosumab with zoledronic acid, disodium pamidronate, ibandronic acid and best supportive care. Zoledronic acid is the primary comparator in patients with breast cancer, with disodium pamidronate and ibandronic acid as secondary comparators. In prostate cancer, for patients with no prior skeletal-related event, the comparator is best supportive care, and in patients with a prior skeletal-related event the comparator is zoledronic acid. In other solid tumours, for patients with no prior skeletal-related event, the

comparator is best supportive care and in patients with a prior skeletal-related event the comparators were zoledronic acid and disodium pamidronate. The model has a 4-week cycle length and a half-cycle correction is applied. Patients are followed for 10 years.

6.3 The same model structure is used for each tumour type, but the absolute and relative risk of skeletal-related events, adverse events and cancer mortality are modelled to reflect the differences between tumour types. The model has 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, as shown in figure 1. Patients enter the model in either of the two 'on treatment' health states, depending on whether or not they have experienced a skeletal-related event. If a patient experiences a skeletal-related event, they can move from a 'no prior skeletal-related event' health state to a 'prior skeletal-related event health state'. If a patient experiences an adverse event and they discontinue treatment, they move from an 'on treatment' health state to an 'off treatment' health state.

Figure 1 Schematic representation of the manufacturer's model structure

SRE: skeletal-related event



6.4 The skeletal-related event risk and event rates were derived from the individual denosumab clinical trials. The risk of skeletal-related event was modelled as a composite outcome, with data then disaggregated into the different skeletal-related event types. 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. In the analysis of patients by prior skeletal-related event history, the baseline event risk differs by patient group. However, the treatment effect is pooled across groups, on the basis that in the trial treatment effect was consistent regardless of skeletal-related event history. Within each tumour type, all patients were assumed to have the same survival risk regardless of treatment.

6.5 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. Five adverse events were selected for inclusion in the model (osteonecrosis of the jaw, renal toxicity, hypercalcaemia, hypocalcaemia and skin infections) based on their impact on cost and/or health-related

quality of life. Discontinuation from treatment was based on the 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.

6.6 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.

6.7 Drug costs were taken from the BNF. Bisphosphonate and denosumab administration costs were derived from a structured questionnaire conducted among appropriate UK healthcare professionals and a subsequent microcosting. It was assumed that bisphosphonates were administered every 4 weeks. Skeletal-related events costs were derived from a prospective observational study (STARS) 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.

6.8 The manufacturer submitted a patient access scheme in which the price of denosumab was [redacted] in parallel with the main submission that provided base-case results for the incremental cost per QALY gained for the following patient groups:

- breast cancer (table 8)
- prostate cancer patients (table 9)
  - with painful bone metastases who have experienced a prior skeletal-related event

  - with no pain or with pain but no history of a prior skeletal-related event
- other solid tumours patients (table 10)
  - with painful bone metastases who have experienced a prior skeletal-related event
  - with no pain or with pain but no history of a prior skeletal-related event.

Table 8 Manufacturer's base-case cost-effectiveness analysis for breast cancer patients with bone metastases

Treatment	Costs (£)	QALYs	Denosumab compared with comparator			
			ΔCosts (£) No PAS/ PAS	ΔQALYs	ICER No PAS	ICER PAS
Denosumab (no PAS) Denosumab (PAS)	[redacted]	1.912	–	–	–	–
Zoledronic acid	[redacted]	1.904	1484/−483	0.007	£203,387	Denosumab dominant
Disodium pamidronate	[redacted]	1.898	−1486/−3453	0.013	Denosumab dominant	Denosumab dominant
Ibandronic acid	[redacted]	1.907	72/−1895	0.005	£13,835	Denosumab dominant
ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; Δ incremental						

Table 9 Manufacturer's base-case cost-effectiveness analysis for prostate cancer

Treatment	Costs (£)	QALYs	Denosumab compared with comparator			
			ΔCosts (£) No PAS/ PAS	ΔQALYs	ICER No PAS	ICER PAS
Patients with painful bone metastases who have experienced a prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	1.089	–	–	–	–
Zoledronic acid	[redacted]	1.083	922/−281	0.006	£157,276	Denosumab dominant
Patients with no pain or pain and no history of a prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	1.189	–	–	–	–
Best supportive	[redacted]	1.150	3993/ 2790	0.039	£102,067	£71,320

care
ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year, Δ incremental

Table 10 Manufacturer's base-case cost-effectiveness analysis for other solid tumours

Treatment	Costs (£)	QALYs	Denosumab compared with comparator			
			ΔCosts (£) No PAS/ PAS	ΔQALYs	ICER No PAS	ICER PAS
Patients with painful bone metastases who have experienced a prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	0.765	–	–	–	–
Zoledronic acid	[redacted]	0.761	757/−43	0.004	£205,580	Denosumab dominant
Disodium pamidronate	[redacted]	0.759	−2118/ −2918	0.006	Denosumab dominant	Denosumab dominant
Patients with no pain or pain and no history of a prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	0.803	–	–	–	–
Best supportive care	[redacted]	0.782	1730	0.021	£122,499	£83,763
ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; Δ incremental						

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

6.10 The Assessment Group noted that the manufacturer's model was of good quality and structure. It highlighted that although the submission suggested subgroups based on prior skeletal-related event experience were included, the clinical trial data specific to the

treatment effect in these groups were not applied. The Assessment Group stated that the rates of adverse events for best supportive care are assumed to be zero and noted that this may worsen the cost-effectiveness estimates relative to best supportive care. The Assessment Group also stated that the manufacturer quoted costs for zoledronic acid that were 5% higher than those listed in BNF 62. It also noted that that microcosting study that was used to estimate administration costs associated with different administration routes might not be reliable because the skewed nature of the replies meant that the manufacturer used median values rather than means for costing purposes. The manufacturer also used 2008–2009 reference costs for radiotherapy planning and administration rather than using 2009–2010 costs that were used for all other skeletal-related events. The Assessment Group also noted that there was no detail about the functional forms that were tested during the EQ-5D data analysis. Further, the model attempted to correct for the fact that benefits before the start of therapy are not projected. However, it appeared that this may cut off the patient benefits in the 5 months following a skeletal-related event occurring in the first cycle of the model, in the 4 months following a skeletal-related event occurring in the second cycle of the model, and so on. It also appeared that the skeletal-related event decrement among patients who had not had a skeletal-related event was measured from the skeletal-related event-naive baseline health-related quality of life for the 5 months after a skeletal-related event, but the patient was modelled as stepping down to the skeletal-related event-experienced health-related quality of life for this period and beyond. This may double-count the impact of first skeletal-related events in the 5 months after their diagnosis.

Assessment Group model

6.11 The Assessment Group used the manufacturer's model as the basis of their economic modelling, rebuilding the model with the

same overall structure. The Assessment Group included analyses of breast cancer, prostate cancer, NSCLC and other solid tumours (including NSCLC). 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 NSCLC outcomes by skeletal-related event history, therefore only an analysis of all patients is presented for this subgroup. The description below highlights the changes made to the manufacturer's model indicating which were included in the base-case analysis and which in sensitivity analyses. Other parameters remained the same.

6.12 The base-case economic analysis applies the results of the Assessment Group's network meta-analysis for time to first skeletal-related event and risk of subsequent skeletal-related event. Other adjustments included in the base-case analysis are to the treatment of utilities in order to adjust for not projecting benefits to before the start of treatment, and to measure any utility decrements subsequent to a skeletal-related event from the skeletal-related event-experienced baseline utility. In addition, the Assessment Group made amendments to the resource data, using the zoledronic acid price and the pamidronate price based on BNF 62. They 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 (table 11).

Table 11 Skeletal-related event and serious adverse-event costs

Skeletal-related events	Assessment Group	Manufacturer
Vertebral fracture	£294	[redacted]
Non-vertebral fracture	£1581	
Radiation to the bone	£662	
Surgery to the bone	£7269	

Spinal cord compression	£7311	[redacted]
Serious adverse events		
Osteonecrosis of the jaw	£1220	£2465
Renal	£496	£1681
Hypercalcaemia	£4579	£4579
Hypocalcaemia	£443	£443
Skin	£370	£1440
[a]£5261 based on average NHS reference costs		

6.13 Other amendments to the model were included in sensitivity analyses only. Additional structural elements included the facility for spinal cord compression to have a sustained health-related quality of life impact beyond 5 months after the compression, and a decay in quality of life in the final year of life. In addition, alternative estimates of time to first skeletal-related event and risk of subsequent skeletal-related event were explored. Finally, the amount of time the utility decrement was applied for osteonecrosis of the jaw and renal toxicity was changed from a permanent decrement to a decrement lasting only the duration of the trial data. Separate analyses are also presented that apply the SRE naive and SRE experienced subgroup data from the denosumab clinical trials, but for the other comparators (those not included in the trials) use the results of the Assessment Group network meta-analysis.

6.14 For the analysis of NSCLC the Assessment Group used its own estimates of time to first skeletal-related event and risk of subsequent skeletal-related event. Overall survival was taken from the estimate for zoledronic acid presented in Joshi (2011). For modelling of NSCLC the discontinuation rates and serious adverse events are assumed to be the same as those for the other solid tumours including NSCLC modelling.

Assessment Group's base case

6.15 The results of the deterministic base-case cost-effectiveness analysis for breast cancer are presented in table 12. With the PAS, zoledronic acid and pamidronate are dominated by denosumab because denosumab is more effective and less costly. Even though

denosumab is more effective than best supportive care, it is more costly and with the PAS denosumab compared with best supportive care has an ICER of £152,847 per QALY gained for all patients. Probabilistic modelling produced similar results.

Table 12 Assessment Group's base-case cost-effectiveness analysis for breast cancer

Treatment	Costs (£)	QALYs	Denosumab compared with comparator			
			ΔCosts (£) No PAS/ PAS	ΔQALYs	ICER (no PAS)	ICER (PAS)
All patients						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	1.846	–	–	–	–
Zoledronic acid	[redacted]	1.833	1680/−270	0.013	£126,821	Dominant
Pamidronate	[redacted]	1.832	−1367/−3317	0.014	Dominant	Dominant
BSC	[redacted]	1.819	6114/4165	0.27	£224,411	£152,847
Patients with no prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	1.883	-	-	-	-
Zoledronic acid	[redacted]	1.868	1726/−225	0.015	£117,186	Dominant
Pamidronate	[redacted]	1.870	−1156/−3106	0.013	Dominant	Dominant
BSC	[redacted]	1.848	6223/4273	0.034	£181,007	£124,291
Patients with prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	1.793	-	-	-	-
Zoledronic acid	[redacted]	1.782	1615/−335	0.011	£145,171	Dominant
Pamidronate	[redacted]	1.776	1670/−3620	0.017	Dominant	Dominant
BSC	[redacted]	1.776	5958/4008	0.017	£350,856	£236,037

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; Δ incremental

6.16 Table 13 presents the results of the deterministic base-case cost-effectiveness analysis for prostate cancer. With the PAS, zoledronic acid is dominated by denosumab and compared with best supportive care denosumab has an ICER of £90,788 per

QALY gained for all patients. Probabilistic modelling produced similar results.

Table 13 Assessment Group's base-case cost-effectiveness analysis for prostate cancer

Treatment	Costs (£)	QALYs	Denosumab compared with comparator			
			ΔCosts (£) No PAS/ PAS	ΔQALYs	ICER (no PAS)	ICER (PAS)
All patients						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	1.097	–	–	–	–
Zoledronic acid	[redacted]	1.077	941/−243	0.020	£46,976	Dominant
BSC	[redacted]	1.068	3880/2695	0.030	£130,674	£90,788
Patients with no prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	1.129	–	–	–	–
Zoledronic acid	[redacted]	1.104	897/−287	0.025	£35,732	Dominant
BSC	[redacted]	1.091	3832/2648	0.038	£100,601	£69,510
Patients with prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	1.012	–	–	–	–
Zoledronic acid	[redacted]	1.006	1061/−123	0.006	£167,503	Dominant
BSC	[redacted]	1.006	4009/2825	0.007	£574,364	£404,707

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; Δ incremental

6.17 The results of the deterministic base-case cost-effectiveness analysis for other solid tumours are presented in table 14. With the PAS, across all patients, the ICER for denosumab compared with zoledronic acid is £12,969 per QALY gained. Against best supportive care in all patients, the ICER for denosumab with the PAS is £137,535 per QALY gained. Probabilistic modelling produced similar results.

Table 14 Assessment Group's base-case cost-effectiveness analysis for other solid tumours

Treatment	Costs (£)	QALYs	Denosumab compared with comparator			
			∆Costs (£) No PAS/ PAS	∆QALYs	ICER (no PAS)	ICER (PAS)
All patients						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	0.715	–	–	–	–
Zoledronic acid	[redacted]	0.708	880/99	0.008	£115,741	£12,969
BSC	[redacted]	0.702	2573/1791	0.013	£197,550	£137,535
Patients with no prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	0.731	–	–	–	–
Zoledronic acid	[redacted]	0.723	892/110	0.008	£113,054	£13,931
BSC	[redacted]	0.711	2482/1700	0.020	£125,301	£85,843
Patients with prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	0.699	–	–	–	–
Zoledronic acid	[redacted]	0.691	868/86	0.007	£118,884	£11,844
BSC	[redacted]	0.693	26711,890	0.006	£470,820	£333,055

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; ∆ incremental

6.18 Table 15 presents the results of the deterministic base-case cost-effectiveness analysis for lung cancer. With the PAS denosumab compared with zoledronic acid has an ICER of £10,099 per QALY gained across all patients. Against best supportive care in all patients the ICER for denosumab is £185,966 per QALY gained. Probabilistic modelling produced similar results.

Table 15 Assessment Group's base-case cost-effectiveness analysis for non-small-cell lung cancer

Treatment	Costs (£)	QALYs	Denosumab compared with comparator			
			∆Costs (£) No PAS/ PAS	∆QALYs	ICER (no PAS)	ICER (PAS)
All patients						

Denosumab (No PAS) Denosumab (PAS)	[redacted]	0.452	–	–	–	–
Zoledronic acid	[redacted]	0.446	738/58	0.006	£127,599	£10,099
BSC	[redacted]	0.443	2317/1637	0.009	£263,132	£185,966
Patients with no prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	0.470	–	–	–	–
Zoledronic acid	[redacted]	0.461	683/3	0.009	£79,694	£382
BSC	[redacted]	0.458	2292/1613	0.012	£198,073	£139,364
Patients with prior skeletal-related event						
Denosumab (No PAS) Denosumab (PAS)	[redacted]	0.433	–	–	–	–
Zoledronic acid	[redacted]	0.430	798/118	0.003	£288,320	£42,698
BSC	[redacted]	0.427	2343/1664	0.006	£403,622	£286,598
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; Δ incremental						

Sensitivity analyses

6.19 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. The results summarised below are those including the PAS.

6.20 For breast cancer in the analyses of 'all patients' compared with zoledronic acid, denosumab remains dominant in all univariate sensitivity analyses. For prostate cancer in the skeletal-related event experienced analysis, in comparison with zoledronic acid,

denosumab remains dominant in all univariate sensitivity analyses. However, in the skeletal-related event naive analysis in comparison with best supportive care, none of the sensitivity analyses report an ICER of less than £30,000 per QALY gained. For the other solid tumours, in the skeletal-related event experienced analysis, in comparison with zoledronic acid, univariate sensitivity analyses suggest that denosumab ranges from being dominant to having an ICER of £23,310 per QALY gained. In the skeletal-related event naive analysis in comparison with best supportive care, the ICERs range from £66,365 to £120,670 per QALY gained. Finally, for NSCLC in the skeletal-related event experienced analysis, in comparison with zoledronic acid, the ICERs for the univariate sensitivity analyses range from £6782 to £108,380 per QALY gained. In the skeletal-related event naive analysis, in comparison with best supportive care, the ICERs for the univariate sensitivity analyses range from £115,483 to £180,325 per QALY gained.

6.21 The Assessment Group state that the ICERs are sensitive to changes in the price of zoledronic acid, with a reduction in price of 20% leading to ICERs for denosumab compared to zoledronic acid of £[redacted], £[redacted], £[redacted] and £[redacted] per QALY gained for breast, prostate, other solid tumours and NSCLC respectively.

6.22 In the analyses by the Assessment Group that that apply the SRE naive and SRE experienced subgroup data from the denosumab clinical trials, and the results of the network meta-analysis for the other comparators, the ICERs are comparable to those in the base-case analysis for breast and prostate cancer. For the other solid tumours using data specific to skeletal-related event history reduces the ICER for the skeletal-related event naive group from £13,931 to £4076 per QALY gained (with the PAS), and increases the ICER for the skeletal-related event experienced group from £11,844 to £38,458 per QALY gained (with the PAS).

6.23 A comparison of the base-case analysis of the Assessment Group and the manufacturer suggests that the results for breast and prostate cancer are comparable across the models. For both breast cancer and prostate cancer the ICERs for denosumab in comparison with zoledronic acid without the PAS are above £30,000 per QALY gained, and with the PAS denosumab is dominant. In comparison with best supportive care the ICERs in both models are above £30,000 per QALY gained both with and without the PAS. For other solid tumours, the results of the manufacturer and the Assessment Group differ when the PAS is applied, but without the PAS the ICERs in both models are above £30,000 per QALY gained. With the PAS in the manufacturer's analysis denosumab is dominant with a cost saving of £43, while in the Assessment Group's analyses the ICERs for denosumab range from £4076 to £38,458 per QALY gained with an additional cost of approximately £900.

7 Equalities issues

7.1 One consultee commented about the sex of patients with prostate and breast cancer. It is not considered that patient sex in prostate cancer reflects an equalities issue. Denosumab will be appraised within its licensed indication and based on the evidence submitted: in relation to breast cancer, if relevant, this could include consideration of equality issues around patient sex.

8 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Lung cancer: the diagnosis and treatment of lung cancer. NICE clinical guideline 121 (2011). Available from www.nice.org.uk/guidance/CG121
- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009). Available from www.nice.org.uk/guidance/CG81
- Metastatic spinal cord compression: diagnosis and management of adults at risk of and with metastatic spinal cord compression. NICE clinical guideline 75 (2008). Available from www.nice.org.uk/guidance/CG75
- Prostate cancer: diagnosis and treatment. NICE clinical guideline 58 (2008). Available from www.nice.org.uk/guidance/CG58