Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

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NB. This protocol may evolve in the course of the review.

Title of the project

Denosumab for the treatment of bone metastases from solid tumours and multiple myeloma.

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Plain English Summary

Cancer can spread from the part of the body where it started (primary site) to other parts of the body; when this happens it is called metastatic disease. For example, when breast cancer spreads to bone it may be called metastatic breast cancer or breast cancer with bone metastasis. The location and extent of metastasis depends on the primary site and the aggressiveness of the cancer.

The bones are a common site of spread in many solid cancers, but especially ones that start in the prostate, breast and lung. Multiple myeloma is another type of cancer affecting the white blood cells and starts in the bone marrow. Specific areas of the bone can be affected, causing similar symptoms to bone metastasis.

Bone metastasis can cause a number of problems. These include:

- Pain: this may be constant or intermittent
- Fractures: long bones with cancer in them may break with minimal or no force
- Compression of the spinal cord: this may happen if a cancer spreads to the bones of the back, if this results in squeezing of the spinal cord. If this happens, it may cause weakness or numbness in the legs or problems with passing urine or bowel opening
- High calcium in the blood stream: cancer in the bone may cause calcium to be released into the bloodstream. High levels of calcium in the bloodstream may cause an individual to become non-specifically unwell, and if left untreated can eventually lead to coma and death.

Therefore, if a cancer spreads to the bones, the quality of life and life expectancy of a patient may be greatly reduced.

Currently the problems caused by bone metastases and multiple myeloma may be treated with a bisphosphonate, such as zoledronic acid, ibandronic acid, disodium pamidronate, or sodium clodronate. They may also be treated with supportive care treatments, including painkillers, radiotherapy and occasionally surgery. The specific place of the bisphosphonates and supportive care treatments for patients with lung cancer, prostate cancer, metastatic spinal cord compression and advanced breast cancer are recommended by NICE in their Clinical Guidelines CG 24, 58, 75 and 81, respectively.

Bisphosphonates are unfortunately not suitable for all patients with bone metastasis. They are associated with renal toxicity and require routine monitoring of serum creatinine and other biochemical parameters and dose adjustments. They are not recommended in patients with severe renal impairment.

The mode of administration of bisphosphonates may also be problematic in clinical use. Zoledronic acid and disodium pamidronate must be administered by intravenous infusion, ibandronic acid can be given either orally or intravenously, and sodium clodronate can be given orally.

Decision problem

Denosumab is a new drug that has been tested in bone metastases and multiple myeloma. It is currently licensed for treatment of thin bones in postmenopausal women and bone loss caused by treatment of prostate cancer (hormone ablation treatment).

Denosumab offers an alternative therapy to bisphosphonates for the prevention of skeletal-related events (SRE). It is not associated with renal toxicity, and can be used in patients taking concomitant nephrotoxic drugs, for whom bisphosphonates cannot be prescribed. Denosumab is also administered as a simple subcutaneous injection, which may allow it to be given in general practitioner surgeries, in hospices, or at the patient's home.

The purpose of this review will be to appraise the clinical effectiveness and cost-effectiveness of denosumab, within its licensed indication, for the treatment of bone metastases from solid tumours and bone disease in multiple myeloma.

We note that there has been no technology appraisal by NICE of the bisphosphonates. We will not review the clinical effectiveness and cost-effectiveness of bisphosphonates relative to best supportive care.

The intervention

The intervention is denosumab, administered every 4 weeks at a dose of 120 mg as a subcutaneous injection in the upper arm, upper thigh or abdomen.

One issue is the place of the denosumab in the treatment pathway. We anticipate this varying depending on the type of cancer, but some possibilities could be:

1. As primary prevention of SREs in patients newly diagnosed with solid malignancies with bone metastases or with multiple myeloma
2. For secondary prevention of further SREs in patients with solid malignancies or those with multiple myeloma who have already suffered a SRE
3. For the active treatment of SREs, including treatment of bone-induced pain and hypercalcaemia
4. As a second-line therapy for SREs in patients for whom best supportive care has not proved adequate or have failed
5. As an alternative treatment in patients unable to tolerate intravenous bisphosphonates, or for whom they are contraindicated.

The comparators

The relevant comparators are: (1) bisphosphonates, and (2) best supportive care.

The bisphosphonates

The bisphosphonates are synthetic analogues of pyrophosphates, the natural regulator of bone mineral precipitation and dissolution. They inhibit normal and pathological osteoclast-mediated bone resorption. Over the past two decades bisphosphonates have established themselves as an important treatment for bone metastases in solid cancers and for multiple myeloma. While denosumab also inhibits osteoclasts, it is thought to be through a different pathway to that of bisphosphonates.

There are currently four bisphosphonates licensed in the UK for bone metastasis or multiple myeloma;

(a) Zoledronic acid (Zometa™, Novartis) is licensed for the reduction of bone damage in advanced malignancies involving bone. It is administered by intravenous infusion over at least 15 minutes at a dose of 4 mg every 3–4 weeks.
(b) Disodium pamidronate (Aredia®, Novartis) is licensed for osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma. It is administered by slow intravenous infusion (at least over 2 hours) at a dose of 90 mg every 4 weeks.
(c) Sodium clodronate (Bonefos™, Bayer Schering; Clasteon™, Beacon; Loron 520™, Roche) is licensed for osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma. It is administered by mouth at a dose of 1.6–3.2 g daily.
(d) Ibandronic acid (Bondronate™, Roche) is licensed for the reduction of bone damage in bone metastases in breast cancer. It is administered either by mouth (50 mg daily) or intravenous infusion (6 mg every 3–4 weeks).

Therefore, only zoledronic acid is licensed in the UK for the reduction of bone damage in all advanced malignancies involving bone.

Unfortunately bisphosphonates are not uniformly effective in reducing skeletal-related events in all types of cancer. There are inconsistencies in the evidence relating to their effectiveness, depending on the site or type of cancer and the bisphosphonate used.

Some patients are contraindicated to bisphosphonates or their use is inappropriate. There is wide variation currently in the use of bisphosphonates for the management of patients with bone metastases in the UK. Patterns of use depend no adoption of local and national guidelines and physician and patient preferences.

Only zoledronic acid and disodium pamidronate are licensed by the US Food and Drug Administration for treatment of bone metastases in the USA.

Zoledronic acid (Zometa) is a very frequently used bisphosphonate in the UK, and is recommended by many clinicians as the bisphosphonate of choice.

Best supportive care

Best supportive care (BSC) will also be considered as a comparator where bisphosphonates are not considered appropriate.

The patient groups included will be adults with bone metastases from solid tumours and adults with myeloma bone disease. The report will separately consider patient groups, based on location or type of primary cancer.

The key aspects that will be addressed will be the clinical effectiveness and cost-effectiveness of denosumab relative to bisphosphonates and/or best supportive care.

Any adverse effects of the treatment will also be addressed.

Identifying comparators

As the guidelines indicate that the place of bisphosphonates in the care pathway differs for each primary tumour type, each type will be treated separately (where data exist). In tumour types where no guidelines exist, we will seek expert opinion as to the place of bisphosphonates in the care pathway.

Breast cancer

As NICE CG81 recommends use of a bisphosphonate in patients with advanced breast cancer newly diagnosed with bone metastases, we will not use BSC as a comparator.

We know from our scoping searches that there are no published Phase III trials of denosumab against comparators other than zoledronate.

We will not assume a class effect for the bisphosphonates. If no high-quality systematic reviews that meet our inclusion criteria exist, we will perform an indirect comparison (as shown in *Figure 1*) to determine the most effective bisphosphonate to compare with denosumab.

Other solid tumours or multiple myeloma

As the NICE guidelines for prostate and lung cancer recommend BSC, before giving a bisphosphonate, then for these patient groups (where data exist) we will include BSC as a comparator.

For other solid tumours and multiple myeloma, where no relevant NICE guidelines exist, we will seek expert opinion as to the place of bisphosphonates in the clinical pathway. If it emerges that bisphosphonates are recommended as first-line therapy for any of these patient groups, then the network diagram will be as in *Figure 1*.

Otherwise we will look for trials against the various comparators to compare with denosumab in an indirect comparison as indicated in the network diagram in *Figure 2*.

Report methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of denosumab for bone metastases from solid tumours and multiple myeloma. A review of the evidence for clinical effectiveness will be undertaken systematically following the principles in the *Centre for Reviews & Dissemination (CRD):CRD's guidance for undertaking reviews in health care: Systematic Reviews (3rd Edition), 2008* and the *Cochrane Handbook for Systematic Reviews of Interventions.*

Criteria for considering studies for the review

Types of studies

Only systematic reviews and randomised controlled trials will be considered for clinical effectiveness. There will be no size restriction on the number of patients in trials, because those with inadequate numbers and hence power, might be useful when combined in a meta-analysis.

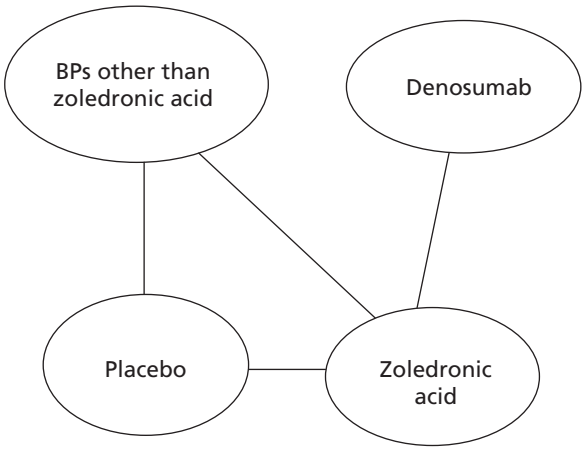

FIGURE 1 Network meta-analysis for those with bone metastases from breast cancer.

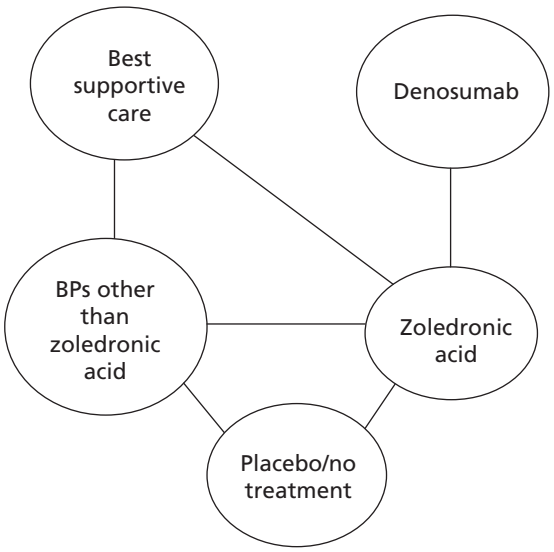

FIGURE 2 Network meta-analysis for those with bone metastases from prostate, lung cancer and other solid tumour.

If there are any high-quality existing systematic reviews that meet our inclusion we will not repeat them, but update them with more recent randomised controlled trials identified from our searches.

We will seek selected clinical study reports from the manufacturer.

Observational studies may be used (in addition to randomised controlled trials) for data on safety.

Types of participants

These will be patients with confirmed carcinoma of any of the below:

- breast
- prostate
- lung
- other solid tumours
- multiple myeloma

plus, evidence of at least one bone metastasis or myeloma bone lesion.

Types of interventions

The intervention is denosumab, given as a subcutaneous injection at dose of 120 mg every 4 weeks. Denosumab does not yet have a marketing authorisation in the UK for the treatment of bone metastases from solid tumours and multiple myeloma. However, it does have a UK marketing authorisation for the treatment of osteoporosis in postmenopausal women and for the treatment of bone loss associated with hormone ablation in men with prostate cancer.

We will exclude studies (such as pharmacokinetic or drug tolerability studies) where patients are only given a single dose of a drug. Also, in studies that have arms with more than one dose of a licensed comparator drug, we will only extract data from the arm that includes the licensed dose of the drug.

Types of comparators

Bisphosphonates

These are: sodium clodronate, disodium pamidronate, ibandronic acid and zoledronic acid. We initially considered including etidronate as an unlicensed (for this purpose) comparator, because of its much lower cost. However, clinical advice is that it is infrequently used because of its gastrointestinal toxicity.

Currently, zoledronic acid has UK marketing authorisation for use in all cancers, disodium pamidronate and sodium clodronate are licensed for breast cancer and multiple myeloma, and ibandronic acid is only licensed for breast cancer. However, we will also include trials of these bisphosphonates when used outside their licensed indications.

Best supportive care (**excluding bisphosphonates)**

This varies depending on the type of cancer. The relevant NICE Clinical Guidelines are: CG58 for prostate cancer and CG24 for lung cancer. The UK Myeloma Forum has issued a guideline for the diagnosis and management of multiple myeloma. All these guidelines recommend radiotherapy and analgesics as best supportive care. Other supportive care for bone metastasis, also recommended, includes surgical fixation in breast cancer and multiple myeloma, strontium-89 in prostate cancer and nerve blocks in lung cancer.

Outcomes

Outcome measures will include

- Time to first on-study skeletal adverse events. These will be defined as: pathological fracture, requirement for radiation therapy to bone, surgery to bone, or spinal cord compression (information on all events will be sought from the manufacturer)
- time to subsequent skeletal adverse events
- incidence of skeletal-related events
- prevention of hypercalcaemia
- overall survival rate
- pain
- health-related quality of life
- adverse events related to treatment (including hypocalcaemia, osteonecrosis of the jaw, renal toxicity).

Search strategy

We will search the following sources:

- MEDLINE
- EMBASE
- The Cochrane Library (all sections)
- Science Citation Index Expanded (SCI expanded) and Conference Proceedings Citation Index- Science (CPCI-S)
- Contact with experts in the field
- Search of ASCO meeting abstracts
- Scrutiny of bibliographies of retrieved papers.

Searches will be limited to those published in the English language.

Only studies published as full text will be data extracted and used to assess clinical effectiveness. Meeting abstracts will be searched for and tabulated for use in the Discussion to indicate ongoing research (for recent abstracts), or possible sources of publication bias (for older abstracts not subsequently published in full).

Study selection

Study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Data extraction strategy

Data will be extracted from the included studies by one reviewer, using a standardised data extraction form and checked by a second. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Quality assessment

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus, and if necessary a third reviewer will be consulted.

The quality of the randomised controlled trials will be assessed by using methods for assessing Cochrane risk of bias and include:

- adequate sequence generation
- allocation concealment
- blinding
- incomplete outcome data addressed
- free of selective reporting
- generalisability

- sample size calculation.

The quality of the systematic reviews will be assessed using quality assessment criteria:

- inclusion criteria described
- details of literature search given
- study selection described
- data extraction described
- study quality assessment described
- study flow shown
- study characteristics of individual studies described
- quality of individual studies given
- results of individual studies shown
- statistical analysis appropriate.

Methods for estimating qualify of life

Quality-of-life data, as reported within the studies identified, the clinical systematic review, the denosumab clinical study reports, and the manufacturer's submission, will be reviewed.

A further systematic review of the effects no quality of life of SREs arising from metastatic bone disease and from myeloma bone disease will be undertaken. There may also be a requirement to review mapping functions from disease-specific quality-of-life functions and/or disease-specific pain scores to generic quality-of-life functions and/or index values.

Economic modelling may require additional quality-of-life values for health states within the underlying cancer(s). The default will be to source these from previous NICE clinical guidelines as outlined above, and only if these are insufficient, to undertake further literature search and review.

Summary statistics as reported within the denosumab clinical study reports and the manufacturer's submission may lead the Technology Assessment Report team to request patient-level data from the manufacturer in order to cross check and possibly separately identify HRQoL values for use within any economic model(s).

Methods of analysis/synthesis

Initially we will look for head-to-head trials of denosumab versus bisphosphonates or BSC. Our initial scoping searches indicate that at present there are only three published Phase III trials of denosumab which include our relevant population, and these all use zoledronic acid as a comparator. The three patient groups included in the three trials are respectively: (1) advanced breast cancer, (2) castration-resistant prostate cancer, and (3) patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma.

Therefore, in order to be able to compare denosumab to bisphosphonates other than zoledronate, or to BSC, we will need to look for trials including these comparators, either head-to-head or against placebo.

Trials that fit our inclusion criteria will be assessed for heterogeneity. The studies will be examined for comparability with respect to methods, baseline characteristics of the intervention groups and measurement of outcome.

If trials are considered sufficiently homogeneous, a mixed treatment comparison of denosumab versus BSC will be carried out. This will pool direct and indirect evidence from randomised trials in a single analysis.

Patient groups will be analysed separately based on location or type of primary cancer. If sufficient data are available, subgroup analyses will be performed to examine the effect of treatment depending on: the

type of SRE, history of SREs**,** prior use of bisphosphonate, prior type of BSC, different adjuvant therapies, different routes of administration of the bisphosphonates, and the location of the metastases.

Report methods for synthesising evidence of cost-effectiveness

A systematic review of cost-effectiveness studies of denosumab for the treatment of bone metastases from solid tumours and multiple myeloma will be undertaken.

If the economics of the manufacturer's submission are insufficient, the modelling underlying this submission may be adapted by the Technology Assessment Report teams or the Technology Assessment Report team may develop a de novo model.

If de novo modelling is required, the NICE reference case will be adopted by the Technology Assessment Report team, including probabilistic modelling. Modelling will adopt a lifetime horizon.

For primary tumours where bisphosphonates are recommended, among those who tolerate bisphosphonates it will be assumed that bisphosphonates are cost-effective and the cost-effectiveness of bisphosphonates relative to BSC will not be reviewed. Should there be a significant proportion of patients who do not tolerate bisphosphonates it may be desirable to undertake a review of effectiveness, as per *Figure 2*. But there is unlikely to be the network of evidence to support this in the patient group under consideration. In these circumstances, a second-best solution may be to identify which other cancer being reviewed that has BSC as a comparator best mirrors the ideal network of evidence for this patient group, and apply the clinical effectiveness estimates from this comparison for this patient group.

For primary tumours where bisphosphonates are not recommended, BSC will be the comparator, with the clinical effectiveness estimates being drawn from a network of evidence as described in *Figure 2*.

Modelling will limit itself to consideration of the impacts no patient quality of life and treatment costs of:

- SRE rates differentiated by type and time, these potentially also having some survival effect
- morbidity with possibly particular attention being paid to pain scores
- hypercalcaemia
- adverse events.

Any significant non-bone activity will be assumed to be reflected in overall survival estimates. Where there is evidence of an overall survival effect, the extent to which this is likely to be due to non-bone activity will be reviewed. If there is not good evidence of a survival effect arising from non-bone activity, the progression of the primary tumour will be assumed to be the same between the arms.

For patient groups in which bisphosphonates are recommended, the review will start by identifying the most effective bisphosphonate. If one bisphosphonate appears to be more effective than the rest, it will be used as the main comparator.

Zoledronic acid goes off patent in March 2013. In the comparisons of denosumab with the bisphosphonates, threshold analyses around the bisphosphonate price will be undertaken for willingness-to-pay values of £20,000 per QALY and £30,000 per QALY, with this also referencing the cost of etidronate.

Costs will be obtained from standard reference costs. A sensitivity analysis of administration costs will use two assumptions about costs in primary care: standard costs, and an enhanced service payment.

Since different cancers behave differently, we will need to review the evidence on clinical effectiveness and cost-effectiveness separately for the main cancers: breast, prostate and lung cancers, and multiple myeloma.

For a primary cancer with an insufficient network of evidence to enable firm conclusions to be drawn about the effectiveness of denosumab relative to the appropriate comparator, it may be possible to assume clinical effects as drawn from the review of denosumab compared to that comparator as estimated within another cancer. These clinical effectiveness estimates could then be applied to the survival estimates for the primary cancer with an insufficient network of evidence. In other words, the only analysis possible will in effect be a sensitivity analysis around patient survival, with some additional variation in the quality-of-life values and costs being applied to health states for the underlying cancer. The credibility of the clinical assumptions necessary for this, and any resultant estimates of cost-effectiveness, will be reviewed in conjunction with expert clinical opinion.

Handling the company submission(s)

All data submitted by the manufacturers/sponsors may be considered if received by the Technology Assessment Report team no later than 22 July 2011. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they may be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided they comply with NICE's advice on presentation and length, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the Technology Assessment Report team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a de novo model.

Any commercial-in-confidence data taken from a company submission, and specified as confidential in the check list, will be replaced in the assessment report with the statement: commercial-in-confidence information has been removed.

Competing interests of authors

Dr Clive Mulatero declares that he has acted in an advisory role to Roche; AstraZeneca; Boehringer Ingelheim and Pierre Fabre; and has had support to attend conferences/meetings or has received bursaries from Roche; AstraZeneca; Boehringer Ingelheim; Lilly and Pierre Fabre.

The other authors declare no competing interests.

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Timetable/milestones

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