NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Denosumab for preventing skeletal-related events in multiple myeloma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of denosumab within its marketing authorisation for preventing skeletal-related events in multiple myeloma.

Background

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells supress the development of normal blood cells that are responsible for fighting infection (white blood cells), carrying oxygen around the body (red blood cells) and blood clotting platelets). The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. The cancer causes destruction of the bones, primarily affecting the spine, pelvis or rib cage, which leads to significant pain and an increase in the risk of fractures.

In 2014, 4,652 people were diagnosed with multiple myeloma in England, with 45% of those people being aged 75 years and over.[1] Around 70% of patients have evidence of myeloma bone disease at the time of diagnosis and approximately 90% of patients have myeloma bone disease at some point during the course of their myeloma.[2]

NICE guideline 35 recommends using zoledronic acid to prevent bone disease in people with myeloma, disodium pamidronate if zoledronic acid is contraindicated or not tolerated, or sodium clodronate if zoledronic acid and disodium pamidronate are contraindicated, not tolerated or not suitable. These treatments are bisphosphonates (bone-protective therapy), which can help prevent myeloma bone disease from getting worse, decrease bone pain and reduce the likelihood of fracture. All bisphosphonates can have serious side effects, including reduced kidney function (renal impairment).

The technology

Denosumab (Xgeva, Amgen) is a fully human monoclonal antibody that targets the receptor activator of nuclear factor kappa-B ligand (RANKL). It prevents RANKL from binding to its receptor RANK, thereby inhibiting osteoclast (the cells responsible for bone resorption) differentiation, activation, and survival. It is administered by subcutaneous injection.

Denosumab does not currently have a marketing authorisation in the UK for preventing skeletal-related events in multiple myeloma. It has been studied in clinical trials compared with zoledronic acid in the treatment of bone disease in adults with newly diagnosed multiple myeloma.

Denosumab has a marketing authorisation for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

Intervention(s)	Denosumab
Population(s)	Adults with multiple myeloma
Comparators	• Zoledronic acid • Disodium pamidronate • Sodium clodronate
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • skeletal-related events • time to first skeletal-related event • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If the evidence allows, subgroups according to renal impairment will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the

	therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours' (2012). NICE Technology Appraisal 265. Review date TBC. Appraisals in development (including suspended appraisals) 'Osteoporotic fragility fractures (prevention) – abaloparatide, raloxifene, strontium ranelate, teriparatide and denosumab' NICE technology appraisals guidance [ID901]. Publication date to be confirmed. 'Bone metastases (hormone refractory prostate cancer) – denosumab' NICE technology appraisals guidance [ID405]. Suspended appraisal. 'Bone loss (therapy-induced in non-metastatic breast cancer) – denosumab [ID83]. Suspended appraisal. Related Guidelines: 'Myeloma: diagnosis and management' (2016). NICE guideline 35. Review date February 2019. Related NICE Pathways Myeloma (2017) NICE pathway
Related National Policy	Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020. https://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 2, 3, 5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for denosumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for preventing skeletal-related events in multiple myeloma?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom denosumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider denosumab will fit into the existing NICE pathway for myeloma?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which denosumab will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider denosumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of denosumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of

appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. We welcome comments on the appropriateness and suitability of the cost comparison methodology to this topic.

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

[1] Cancer Research UK 'Myeloma incidence statistics'. Accessed June 2017.
[2] Myeloma UK 'Myeloma bone disease and bisphosphonates'. Accessed June 2017.