NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Denosumab for prolonging bone metastasis-free survival in hormone-refractory prostate cancer

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of denosumab within its licensed indication for prolonging bone metastasis-free survival in hormone-refractory prostate cancer.

Background

Prostate cancer is a disease in which tumours develop in the prostate, a gland in the male reproductive system. In England and Wales, over 33,000 men were newly diagnosed with prostate cancer, and over 9100 men died from prostate cancer in 2008. The incidence of prostate cancer increases with age and is more common in older men, with around 20% of diagnoses in men under the age of 65 years. The cause of prostate cancer is thought to be multifactorial, involving both environmental and genetic factors.

Prostate cancer growth is stimulated by androgens (male sex hormones) and men with the disease therefore may receive hormone therapy to reduce androgen levels. Most newly diagnosed prostate cancers are initially hormone-dependent and are treated with hormone-ablative therapy. Over time they can progress and become resistant to hormone treatments (hormone-refractory or androgen independent disease). Metastatic disease refers to cancer that has spread from the primary site to other parts of the body. When cancerous cells break away from the primary site, they can travel to other areas of the body through the bloodstream or lymphatic channels. Solid tumours, such as prostate cancer, frequently progress to bone metastases.

NICE clinical guideline 58 (‘Prostate cancer’) states that men with localised disease should be managed with active surveillance, surgical removal of the prostate (known as prostatectomy) or high-dose radical radiotherapy. However, once the cancer has become metastatic, it is unlikely that it will be able to be cured, though the progression of the cancer can be slowed with treatment. Stopping the body making testosterone can slow the growth of the cancer, or even shrink it. Men with prostate cancer may therefore receive hormonal therapy to reduce androgen levels. Standard hormonal treatments for metastatic disease are orchidectomy (surgical removal of the testes, also known as ‘surgical castration’) or use of a gonadotrophin-releasing hormone analogue such as goserelin, leuprorelin or triptorelin (also known as ‘medical castration’).

Between 70-80% of men present with non-metastatic prostate cancer. Of these, approximately 55% to 60% progress to metastatic disease. The prognosis is poor for men with hormone-refractory metastatic prostate cancer; survival is not expected to exceed 15 months. The aim of treatment at this point is to alleviate symptoms, prolong life and slow progression of the disease. NICE Technology Appraisal No. 101 recommends docetaxel as a treatment option for men with hormone-refractory metastatic prostate cancer who have a Karnofsky performance-status score of 60% or more. For men with hormone-refractory metastatic prostate cancer that has progressed during or after a docetaxel-based treatment, patients may receive a combination of palliative treatments.

The technology

Denosumab (Prolia, Amgen) is a fully human monoclonal antibody that specifically targets the receptor activator of nuclear factor kappa B ligand (RANKL) which plays a role in bone destruction and tumour growth in metastatic cancers. It is intended to inhibit osteoclast differentiation, activation and survival, and consequently suppresses bone resorption. Denosumab is administered as a subcutaneous injection.

Denosumab does not hold a UK marketing authorisation for prolonging bone metastasis-free survival in men with hormone-refractory prostate cancer. It has been studied in a clinical trial compared with placebo to prolong bone metastasis-free survival (that is, time to first occurrence of bone metastasis or death) in men with hormone-refractory (androgen independent) non-metastatic prostate cancer who are considered to be at high risk for the development of bone metastases. The trials define individuals as high risk of bone metastases if their prostate specific antigen (PSA) level is greater than or equal to 8.0ng/mL, or their PSA level doubles within 10 months.

Intervention(s)	Denosumab
Population(s)	Men with non-metastatic hormone-refractory prostate cancer at high risk of developing bone metastases
Comparators	• Best supportive care
Outcomes	The outcome measures to be considered include: • time to first occurrence of bone metastasis • overall survival • 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.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 194, July 2010, 'Denosumab for the treatment of therapy-induced bone loss in non-metastatic prostate cancer'. Terminated appraisal. Related Guidelines: Clinical Guideline No. 58, February 2008, 'Prostate Cancer: diagnosis and treatment'. Review date February 2011. Related Public Health Guidance: Cancer Service Guidance, September 2002. 'Improving outcomes in urological cancers'.

Questions for consultation

Where does denosumab for prolonging bone metastases-free survival fit into the current treatment pathway for hormone-refractory prostate cancer? Is this treatment for non-metastatic disease only? If so, what is the clinical consensus on the current treatment of non-metastatic hormone-refractory prostate cancer?

What is the size of the potentially eligible patient population in UK clinical practice?

How should hormone-refractory prostate cancer be defined?

Should high risk of bone metastases be included in the population of the scope, and how should it be defined?

Is best supportive care the most appropriate comparator for denosumab for prolonging bone metastases-free survival in men with hormone-refractory prostate cancer? How should best supportive care be defined?

- Are anti-androgens commonly used to delay the onset of metastases in people with hormone-refractory prostate cancer in the UK? If so, which agents are commonly prescribed?

- Should chemotherapy (with or without corticosteroids) be included as a comparator?

Are the outcomes included in the scope appropriate? Are there any other outcomes that should be included in the scope?

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

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the remit or scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

Do you consider the technology 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 the technology 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.

Denosumab for the treatment of therapy-induced bone loss in non-metastatic prostate cancer is subject to terminated NICE guidance (No. 194). Are the populations in guidance No. 194 and the proposed appraisal of denosumab for prolonging bone metastasis-free survival similar? If they are similar patient populations should NICE combine these appraisals in a single appraisal in order to consider all health effects relevant to patients?

NICE welcomes comments on the appropriateness of appraising this topic through the Single Technology Appraisal (STA) process or the Multiple Technology Appraisal (MTA) process, either alone or combined with a re-appraisal of denosumab for the treatment of therapy-induced bone loss in non-metastatic prostate cancer. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)

Appendix B