Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CDEC FINAL RECOMMENDATION

DENOSUMAB
(Xgeva – Amgen Canada Inc.)
Indication: Prevention of Skeletal-related Events due to Bone Metastases from Solid Tumours

This document was originally issued on November 16, 2011. It was corrected on December 5, 2011. First on-study SRE results were clarified in the first bullet, under the heading "Efficacy" on page 3.

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that denosumab be listed for the prevention of skeletal-related events (SREs) in patients with castrate-resistant prostate cancer (CRPC) with one or more documented bony metastases and good performance status (ECOG performance status score of 0, 1, or 2), in jurisdictions that list zoledronic acid for the same indication.

Reasons for the Recommendation:

1. In three double-blind randomized controlled trials (RCTs) in patients with bony metastases secondary to solid tumours, denosumab was superior (study 103 and study 136) or non-inferior (study 244) to zoledronic acid for outcomes related to SREs (composite of fracture, spinal cord compression, and the need for surgery or radiation therapy of symptomatic bone metastases).
2. Based on the manufacturer's cost-utility analysis, denosumab is cost effective in comparison with zoledronic acid in CRPC, resulting in lower incremental costs and greater incremental quality-adjusted life-years (QALYs). The cost-effectiveness of denosumab in other solid tumours is not known.
3. The incremental cost per QALY for denosumab compared with no treatment in CRPC is $111,000.

Background:
Xgeva has a Health Canada indication for reducing the risk of developing SREs in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours.

It is available as a 120 mg single use, subcutaneous injection and the Health Canada recommended dose is 120 mg every four weeks.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of denosumab and a critique of the manufacturer's pharmacoeconomic evaluation. No patients groups responded to the CDR Call for Patient Input.

Clinical Trials
The CDR systematic review included three manufacturer-sponsored, non-inferiority RCTs. All three trials used a double-blind, double-dummy design to compare denosumab with zoledronic acid for reducing the risk of SREs in cancer patients with bone metastases. The study populations included patients with CRPC (study 103; N = 1,904), breast cancer (study 136; N = 2,046), and patients with advanced cancers including solid tumours, multiple myeloma, and lymphoma, but excluding breast and prostate cancer (study 244; N = 1,779).

In all three trials, the patients received either denosumab 120 mg subcutaneously every four weeks, or zoledronic acid 4 mg intravenously every four weeks. The dose of zoledronic acid was adjusted for patients with baseline creatinine clearance of < 60 mL per minute. Study visits occurred every four weeks. The duration of all three trials was event driven and the data cut-off date for the primary efficacy analysis was after 745 subjects experienced an on-study SRE.

All three trials required patients to have current or prior radiographic evidence of ≥ 1 bone metastasis; an ECOG performance status score of 0, 1, or 2; and creatinine clearance of ≥ 30 mL per minute. Enrolled patients had good performance status; the percentage of patients with an ECOG of 0 or 1 was more than 90% in studies 103 and 136, and more than 80% in study 244. Patients with current or prior intravenous bisphosphonate administration and current or prior oral bisphosphonate use for the treatment of bone metastases were excluded from all trials.

The following percentages of patients had discontinued denosumab or zoledronic acid treatment prior to the study cut-off dates: 76% and 79%, respectively, in study 103; 56% in both treatment groups in study 136; and 80% in both treatment groups in study 244. In all trials, death was the most common reason for discontinuation in both treatment groups.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed SREs, quality of life, pain, disease progression, overall survival, serious adverse events, adverse events, and withdrawal due to adverse events. The primary outcome in all three trials was time to first on-study SRE. Subjects who experienced an SRE continued on the study treatments and a multiple-event analysis (time to first and subsequent on-study SRE) was performed as a secondary endpoint.

SREs were defined as one or more of the following: pathological fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression. Symptomatic SREs included pathological fractures and spinal cord compressions that were symptomatic per investigator's evaluation, all surgery to bone, and all radiation to bone.

In all studies, quality of life was assessed using the European Quality of Life – 5 Dimensions questionnaire (EQ-5D) and the Functional Assessment of Cancer Therapy – General (FACT-G).

Studies 103 and 136 also included functional assessments specific to prostate and breast cancer, respectively: FACT-P and FACT-B. Pain was assessed using the Brief Pain Inventory Short Form in all trials.

Results

Efficacy

- Compared with zoledronic acid, denosumab statistically significantly delayed the time to first on-study SRE in both CRPC (study 103) and breast cancer (study 136); hazard ratio (HR) (95% confidence interval [CI]): 0.82 (0.71 to 0.95) for both studies. The median time to first on-study SRE in the denosumab and zoledronic acid treatment groups was 20.7 and 17.1 months, respectively, in CRPC; and non-estimable and 26.4 months, respectively, in breast cancer. Denosumab was non-inferior to zoledronic acid in terms of time to first on-study SRE in advanced cancers (study 244). In all studies, the above findings were consistent across all four components of the composite SRE outcome.
- There were no statistically significant between-treatment differences in quality of life in patients with breast cancer (study 136) and the few statistically significant between-treatment differences in quality of life measures in CRPC (study 103) and advanced cancers (study 244) were of uncertain clinical importance.
- There were no statistically significant differences between the denosumab and zoledronic acid groups in any of the trials with respect to the following assessments: pain; overall survival; overall disease progression excluding death due to any cause; overall disease progression including death due to any cause; and disease progression in bone.

Harms (Safety and Tolerability)

- The incidences of adverse events, serious adverse events, and fatal adverse events were similar between treatment groups in all trials.
- The percentage of patients with hypocalcemia was consistently higher for denosumab compared with zoledronic acid in all trials; 12.8% versus 5.8%, 5.6% versus 3.5%, and 10.8% versus 5.8% for trials 103, 136, and 244, respectively.
- Osteonecrosis of the jaw (ONJ) was infrequently observed but was more common among denosumab-treated patients compared with zoledronic acid in studies 103 and 136 (2.3% versus 1.3% and 2.0% versus 1.4%, respectively) but more common for the zoledronic acid group compared with denosumab in study 244 (1.3% versus 1.1%, respectively).
- Adverse events associated with renal toxicity and acute phase reactions were more commonly reported in patients treated with zoledronic acid than in patients receiving denosumab.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing denosumab with zoledronic acid in patients with CRPC with metastases to the bone over a lifetime time horizon (~11 years). The probabilities of developing a SRE, adverse event, or discontinuation of active treatment were obtained from primary data from Study 103. The manufacturer reported that denosumab led to lower incremental costs and greater incremental QALYs; it was dominant compared with zoledronic acid.

Two key issues were identified. Zoledronic acid is listed in many but not all jurisdictions. If the model is modified to compare denosumab with placebo, use of denosumab is associated with

an incremental cost per QALY gained of $111,000 compared with no treatment. In addition, the cost and cost-effectiveness of denosumab for the treatment of other metastatic cancers, such as breast and lung, are not known.

Drug acquisition costs are the same for denosumab and zoledronic acid ($538 per administration; $7,000 annually) if both are administered every four weeks. Due to the intravenous route, zoledronic acid is associated with greater administration costs.

Patient Input Information:
No patient groups responded to the CDR Call for Patient Input.

Other Discussion Points:
- The Committee noted that the cost-effectiveness of zoledronic acid compared with no treatment in CRPC is unknown.
- The Committee noted that patients with risk factors for ONJ were excluded from the reviewed trials, which may underestimate the risk of this outcome in clinical practice.
- The following are sometimes considered SREs, but were not included in the composite SRE outcome: (1) skeletal instability and/or loss of skeletal integrity, and (2) hypercalcemia.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

October 19, 2011 Meeting

Regrets:
One CDEC member did not attend

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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