



Canadian Drug Expert Committee Final Recommendation – Plain Language Version

DENOSUMAB

(Xgeva – Amgen Canada Inc.)

Indication: Prevention of Skeletal-related Events due to Bone Metastases from Solid Tumours

This document reflects the revision that was made to the technical version of the Final Recommendation on December 5, 2011.

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that denosumab, which is also called Xgeva, be listed by Canada's publicly funded drug plans for the prevention of skeletal-related events (SREs) in patients with castrate-resistant prostate cancer (CRPC) with metastases to the bone (spread of cancer to the bone) and good performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of 0, 1, or 2), in jurisdictions that list zoledronic acid (also called Zometa) for the same indication.

Reasons for the Recommendation:

1. In three medical studies of patients with solid (i.e., not in the blood) tumours and metastases to the bone, Xgeva was either better (study 103 and study 136) or not worse (study 244) than zoledronic acid at decreasing the rate of SREs (an SRE was any of: bone fracture, spinal cord compression, or surgery or radiation to the bone due to bone metastases).
2. Based on the manufacturer's economic evaluation, Xgeva is cost effective compared with zoledronic acid in CRPC. The cost-effectiveness of Xgeva in other solid tumours is not known.
3. Denosumab is unlikely to be cost effective compared with no treatment in CRPC.

Background:

Xgeva belongs to a class of drugs called receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors. Xgeva works differently from other medications used to treat cancer patients whose disease has spread to their bones. RANKL is a protein that promotes the breakdown of bone. Xgeva blocks RANKL to stop the breakdown of bone. This action strengthens the bones by increasing bone mass and lowers the chance of the cancer causing problems with the bones, such as fractures or severe pain requiring radiation treatment.

Plain Language Recommendation

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. Xgeva is not used for reducing the risk of developing SREs in patients with multiple myeloma.

Xgeva is available as liquid in vials. Each vial contains 120 mg of Xgeva. The dose recommended by Health Canada is 120 mg subcutaneously (injection under the skin) every four weeks.

Summary of CDEC Considerations:

To make its decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Xgeva and a review of economic information prepared by the manufacturer of Xgeva. No patient groups responded to the CDR Call for Patient Input.

Clinical Trials

CDEC reviewed three medical studies of patients with cancer that had spread to the bone. These studies were paid for by the manufacturer of Xgeva. The studies looked to see if Xgeva was not worse than zoledronic acid for reducing the risk of SREs in cancer patients with bone metastases. The studies included patients with CRPC (study 103, with 1,904 patients); breast cancer (study 136, with 2,046 patients); and patients with advanced cancers including solid tumours, multiple myeloma, and lymphoma, but not including breast and prostate cancer (study 244, with 1,779 patients).

In all three studies, the patients received either Xgeva 120 mg subcutaneously every four weeks, or zoledronic acid 4 mg by intravenous (into the vein) injection every four weeks. The dose of zoledronic acid was adjusted for patients with low kidney function. Study visits occurred every four weeks. Study duration depended upon when the study cut-off date was reached; the cut-off date was reached when a total of 745 patients had an SRE (while participating in the study).

All three studies required that patients have at least one bone metastasis on an x-ray, and an ECOG performance status score of 0, 1, or 2. The ECOG performance status is a score (from 0 to 5) that measures patients' ability to perform their daily tasks, including work; lower scores mean better ability. In addition, patients were required to have a creatinine clearance of at least 30 mL per minute (indicates sufficient kidney function). Patients in the studies had a 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 who had taken or were currently taking bisphosphonates, either intravenously or by mouth, for the treatment of bone metastases were not included in any of the studies.

The following percentages of patients had stopped taking Xgeva or zoledronic acid treatment before the cut-off date: 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 studies, death was the most common reason to stop taking part in the study, regardless of which treatment the patient was receiving.

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed SREs, quality of life, pain, worsening of disease, overall survival, serious side effects, side effects, and stopping taking part in the study because of side effects. The main result in all of the three studies was the time it took for the patient to have their first SRE while in the study. Patients who had an SRE continued on the study treatments and a second analysis was carried out to look at any further SREs that the patient had while in the study.

SREs were defined as one or more of the following: fracture (either in the spine or elsewhere), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression. Symptomatic SREs included one or more of fractures or spinal cord compression that caused noticeable symptoms to patients, all bone surgeries, and all radiation treatments to the bone.

In all studies, quality of life was measured using the European Quality of Life – 5 Dimensions (EQ-5D) questionnaire 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 measured using the Brief Pain Inventory Short Form in all studies.

Results

Efficacy or Effectiveness

- Compared with zoledronic acid, Xgeva delayed the time to first SRE in both CRPC (study 103) and breast cancer (study 136). The average time until the first SRE for patients in the Xgeva and zoledronic acid groups was 20.7 and 17.1 months, respectively, in CRPC. In the breast cancer study, the average time until the first SRE was 26.4 months in the zoledronic acid group, but could not be calculated in the Xgeva group because not enough patients had an SRE. Xgeva was not worse than zoledronic acid, in terms of time to first SRE, in advanced cancers (study 244). In all studies, the above results were similar when each component of the SRE outcome was looked at separately.
- Quality of life was similar for the breast cancer patients (study 136), regardless of which treatment they received. It was not certain whether the few differences in quality of life scores that were seen in CRPC patients (study 103) and in patients with advanced cancers (study 244) would be important to patients.
- There were no differences between Xgeva and zoledronic acid in any of the studies for the following: pain; overall survival; overall disease worsening, not counting death due to any cause; overall disease worsening including death due to any cause; and disease worsening in bone.

Harms (Safety and Tolerability)

- The amount of side effects, serious side effects, and side effects causing death was similar between treatment groups in all studies.
- The percentage of patients with low levels of calcium in the blood was higher for Xgeva compared with zoledronic acid in all studies: 12.8% versus 5.8%, 5.6% versus 3.5%, and 10.8% versus 5.8% for studies 103, 136, and 244, respectively.
- Osteonecrosis of the jaw (ONJ; a condition where the bone of the jaw breaks down) was not seen very often, but more often among Xgeva-treated patients than among those on

Plain Language Recommendation

zoledronic acid in studies 103 and 136 (2.3% versus 1.3%, and 2.0% versus 1.4%, respectively), but more often for the zoledronic acid group than for Xgeva in study 244 (1.3% versus 1.1%, respectively).

- Side effects of kidney problems and acute phase reactions (fever and other symptoms from taking the medication for the first time) were more commonly seen in patients treated with zoledronic acid than in patients receiving Xgeva.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to evaluate the health benefit of Xgeva compared with zoledronic acid in patients with CRPC and metastases to the bone over a lifetime time horizon (approximately 11 years). The chances of developing an SRE, having a side effect, or of stopping treatment were as seen in study 103. The manufacturer reported that, compared with zoledronic acid, treatment with Xgeva would result in lower costs and greater improvements in quality of life for patients with CRPC.

Two key issues were identified. Zoledronic acid is listed in many, but not all, jurisdictions. If the economic analysis is changed to compare Xgeva with no treatment (represented by placebo, an injection containing no active medication), Xgeva is unlikely to be cost effective. In addition, the cost and cost-effectiveness of Xgeva for the treatment of other metastatic cancers such as breast and lung are not known.

Xgeva costs the same as zoledronic acid (\$538 per administration; \$7,000 per year) if both are administered every four weeks. Because zoledronic acid is given intravenously, it has higher administration costs than Xgeva.

Patient Input Information

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

Other Discussion Points:

- The Committee noted that it is not known if zoledronic acid, compared with no treatment, is cost effective in CRPC.
- The Committee noted that patients with risk factors for ONJ were not included in the reviewed studies; thus the studies may underestimate the risk of ONJ happening when the drug is used in everyday practice.
- The following are sometimes considered SREs, but were not included in the list of outcomes considered to be SREs in the studies: (1) lack of bone stability and/or loss of bone strength, and (2) high blood calcium level.

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, Dr. Adil Virani.

October 19, 2011 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None

About this Document:

The information contained within this plain language version of the Canadian Drug Expert Committee (CDEC) Recommendation about this drug is based on the information found within the corresponding technical version of the CDEC Recommendation.

In making its recommendation, CDEC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the [CDR Drug Database](#) on the CADTH website (www.cadth.ca).

Background on CDEC

CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CDEC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CDEC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.