CADTH CANADIAN DRUG EXPERT REVIEW COMMITTEE FINAL RECOMMENDATION

DENOSUMAB
(Xgeva — Amgen Canada)
Indication: Prevention of Skeletal-Related Events due to Bone Metastases From Breast Cancer

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that denosumab be listed for reducing the risk of developing skeletal-related events in patients with bone metastases from breast cancer, if the following conditions are met:

Conditions:
- List in a manner similar to intravenous (IV) bisphosphonates.
- Reduction in price to improve the cost-effectiveness of denosumab to a level acceptable to the jurisdictions.

Reasons for the Recommendation:
1. In one double-blind, randomized controlled trial (RCT; Study 136) enrolling patients with bone metastases from breast cancer, denosumab was superior to zoledronic acid for time to first skeletal-related event (SRE; hazard ratio [HR] 0.82; 95% confidence interval [CI], 0.71 to 0.95).
2. The CADTH Common Drug Review (CDR) estimated that the incremental cost-utility ratio (ICUR) for denosumab compared with zoledronic acid or pamidronate ranges from $195,000 to $400,000 per quality-adjusted life-year (QALY) if the drug plan funds the cost of the infusion and $395,000 to $710,000 per QALY if the manufacturer funds the cost of the infusion. Therefore, a reduction in price is required for denosumab to be considered a cost-effective treatment option.
3. Although there are no direct comparisons to other bisphosphonates, an indirect comparison suggested that pamidronate is unlikely to be superior to denosumab.

Of Note:
- Patients in Study 136 had not been previously treated with a bisphosphonate for reducing the risk of developing SREs due to bone metastases. The efficacy and cost-effectiveness of denosumab for patients who have failed bisphosphonate therapy are unknown.
- There are no data to assess the comparative clinical and cost-effectiveness of denosumab versus oral bisphosphonates for patients with bone metastases due to breast cancer.

- Individual jurisdictions need to identify the appropriate comparator considering their current listing status for IV bisphosphonates and whether they fund infusion costs associated with these products.

Background:
Denosumab 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. The recommended dose of denosumab is one 120 mg subcutaneous (SC) injection every four weeks.

In response to a request from the CDR-participating drug plans, the manufacturer of denosumab indicated that it was not willing to file a CDR submission for this indication. Therefore, the current CDR submission was filed by the CDR-participating drug plans in order to address the need for a review of the evidence and a formulary listing recommendation from CDEC on the use of denosumab in patients with breast cancer.

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of denosumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients with bone metastases from breast cancer.

Patient Input Information
Three patient groups responded to the CDR call for patient input: the Canadian Cancer Survivor Network, the Canadian Breast Cancer Network, and Rethink Breast Cancer. Information was obtained from surveys, literature review, and interviews. The following is a summary of key information provided by the patient groups:

- Bone metastasis has many serious physical, psychological, social, and financial consequences, including bone pain, weakness, fractures, insomnia, and spinal compression, which were identified as the most difficult consequences to control.
- With the limitations of current treatments on rates of survival, patients with a diagnosis of metastatic cancer seek to live their remaining time with the best possible quality of life.
- The consequences of weakness, fatigue, and pain extend further to affect social and financial aspects of patients' lives, including the ability to work or take care of their children, to engage in family and social events, and to spend quality time with loved ones.
- Caregivers are also affected as they are experiencing anxiety, fatigue, problems with concentration, depression, insomnia, and restrictions in their ability to work or to take care of children and dependants and to participate in social events and activities.
- Bisphosphonates are the usual treatment option, but are associated with severe flu-like symptoms and renal complications. Many patients find the adverse events intolerable and desire alternative therapies that would allow for a greater quality of life.

Clinical Trials
The CDR systematic review included one double-blind RCT. Study 136 (N = 2,046) evaluated the non-inferiority and superiority of denosumab compared with zoledronic acid based on the first occurrence of an SRE in patients with advanced breast cancer and bone metastases. All

patients were strongly recommended to receive concomitant treatment with calcium (≥ 500 mg) and vitamin D (≥ 400 international units [IU]).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Time to first SRE — defined as the first event of any of the following: pathological fracture (vertebral or non-vertebral), radiation therapy to bone, surgery to bone, or spinal cord compression.
- First-and-subsequent SREs — patients who experienced an SRE continued on the study treatments and a multiple-event analysis (time to first-and-subsequent on-study SRE) was performed. To be included in the analysis, subsequent events had to occur ≥ 21 days after the previous SRE, to ensure that potentially related events, such as surgical procedures for a fracture that are likely scheduled within 21 days, were not counted as separate events.
- Brief Pain Inventory (Short Form) (BPI-SF) — a questionnaire used to assess the intensity of pain (pain severity) and the degree to which pain interferes with function (pain interference).
- Functional Assessment of Cancer Therapy–Breast (FACT-B) — a questionnaire consisting of the 27-item Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire with 10 additional questions specific to breast cancer. The questionnaire evaluates physical well-being, functional well-being, social/family well-being, and emotional well-being in patients with cancer.
- Analgesic use — scored on a numerical scale ranging from 0 (no analgesic) to 7 (strong opioids) based on oral morphine equivalent per day.
- EuroQol 5-Dimensions Questionnaire (EQ-5D) — a generic health-related quality of life instrument composed of six questions allowing for estimation of health utility. The first five questions address various quality of life dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety /depression. The last question is represented by a visual analogue scale (EQ-5D VAS), scored from 0 to 100, upon which patients mark their health state.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary efficacy outcome for Study 136 was the time to the first occurrence of an SRE.

Efficacy

- Denosumab was superior to zoledronic acid for reducing the risk of a first SRE in patients with advanced breast cancer and bone metastases. HRs for denosumab versus zoledronic acid were:
  - Full analysis set (FAS): 0.82 (95% CI, 0.71 to 0.95); $P < 0.0001$ for non-inferiority and $P = 0.0101$ for superiority
  - [redacted].
- Denosumab was associated with an improvement in the median time to first on-study SRE of five months, which is likely clinically meaningful to patients according to patient group input, the literature, and the clinical expert consulted by CDR.
- Denosumab was superior to zoledronic acid for time to first-and-subsequent SREs. Rate ratios for denosumab versus zoledronic acid were:
  - FAS: 0.77 (95% CI, 0.66 to 0.89): [redacted] for superiority

  - [redacted].
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Denosumab was associated with a statistically significant reduction in the risk of a > 4-point change in BPI-SF compared with zoledronic acid ([redacted]).
- [redacted]

Harms (Safety and Tolerability)

- Deaths during the trial were reported for [redacted] of patients in the denosumab group and [redacted] of patients in the zoledronic acid group. The most frequently reported causes of death were [redacted].
- At least one serious adverse event was reported for 44% of patients in the denosumab group and 47% of patients in the zoledronic acid group. The most commonly reported serious adverse events were dyspnea, metastases to central nervous system, vomiting, anemia, pleural effusion, hepatic failure, pyrexia, nausea, and metastases to liver.
- At least one adverse event was reported for 96% and 97% of patients in the denosumab and zoledronic acid treatment groups, respectively. The most commonly reported were nausea, fatigue, arthralgia, back pain, diarrhea, dyspnea, vomiting, pain in extremities, and bone pain.
- Osteonecrosis of the jaw was infrequently observed but was numerically more common among denosumab-treated patients compared with zoledronic acid-treated patients (2.0% versus 1.4%, 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.
- Withdrawals due to adverse events were reported for 10% and 12% of patients in the denosumab and zoledronic acid treatment groups, respectively.

Cost and Cost-Effectiveness

As this review was initiated by the CDR-participating drug plans, the manufacturer of denosumab was not obligated to provide economic information. However, the manufacturer supplied a copy of the electronic economic model and report submitted to Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) in 2011 for breast cancer, as well as some other relevant information submitted to other health technology assessment agencies. CDR considered the supplied economic model appropriate for review, although some inputs required updating or revision.

The three-state Markov model compared denosumab primarily with zoledronic acid for advanced breast cancer patients with bone metastases from the Quebec health care payer

perspective over a patient lifetime time horizon (~15 years); a scenario analysis comparing denosumab with pamidronate was also presented. Efficacy, safety, and discontinuation data for denosumab and zoledronic acid were obtained from a single head-to-head study (Study 136). Data for pamidronate were from an indirect treatment comparison. Utility values were obtained from Study 136. Costs and resource use were obtained from sources including the Régie de l'assurance maladie du Québec (RAMQ) and expert input, and reported in 2011 Canadian dollars. The cost of denosumab was equal to that of zoledronic acid. Generic zoledronic acid was not available at the time of analysis. The manufacturer reported that denosumab was associated with lower costs and more QALYs than zoledronic acid and pamidronate from the Quebec health care payer perspective.

CDR updated drug, administration, and monitoring costs to those of provinces participating in the CDR process. CDR considered that the model was associated with uncertainty regarding rates, costs, and utilities for SREs for the comparison with zoledronic acid. CDR noted that the efficacy of pamidronate compared with denosumab may have been underestimated but was not assessed due to the paucity of appropriate data. The CDR clinical review noted that, although denosumab was at least as effective as pamidronate, superiority of denosumab was not proven. Therefore, a cost analysis or cost-minimization analysis may have been more appropriate. No published literature was identified to assess the comparative efficacy of denosumab and clodronate; thus there is uncertainty regarding the comparative efficacy of these drugs.

CDR undertook revised analyses where possible; however, several limitations could not be assessed, including uncertainty around the way SREs are modelled and costed, the time horizon, and the comparison of denosumab with clodronate:

- CDR analyses demonstrated that the ICURs for denosumab (pre-filled syringe) compared with generic zoledronic acid (infusion) or generic pamidronate (infusion) were greater than $395,000 per QALY, assuming the manufacturer funds the infusion costs.
- If the jurisdiction funds the infusion costs, the ICURs for denosumab versus generic zoledronic acid or generic pamidronate are still greater than $195,000 per QALY.
- Assuming the manufacturer funds the infusion costs, a price reduction of 50% would result in ICURs of approximately $100,000 per QALY for denosumab versus generic zoledronic acid or generic pamidronate; and a 60% price reduction would result in denosumab dominating generic zoledronic acid and an ICUR of $60,000 per QALY versus generic pamidronate.
- The results of CDR analyses were supported by the published literature.

Denosumab (Xgeva) is available as a 120 mg/1.7 mL single-use vial of solution for injection at a cost of $575.55 per vial (Ontario Drug Benefit, December 2015). At the recommended dose of 120 mg/1.7 mL every four weeks, the annual cost of denosumab is $7,482 per patient, which is greater than generic zoledronic acid ($2,521 to $3,361 in Alberta), generic pamidronate ($1,182 to $1,577 in Alberta), and clodronate ($2,859 to $5,718 in Alberta). The annual cost of denosumab ($7,482 per patient) is similar to that of branded zoledronic acid ($7,203 to $9,604) and branded pamidronate ($6,510 to $8,680).

Other Discussion Points:
CDEC noted the following:

- The results of an indirect comparison suggested that denosumab is superior to zoledronic acid and placebo, and at least as effective as pamidronate, for reducing the risk of a first SRE in patients with advanced breast cancer and bone metastases, although these findings are associated with a high degree of uncertainty.
- The SC administration of denosumab, compared with zoledronic acid that needs to be administered by IV infusion, provides benefits in terms of accessibility and convenience, often eliminating the need for a visit to a facility for administration.
- Confounding factors may have limited the ability to observe differences between denosumab and zoledronic acid for improving pain and health-related quality of life.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- There are no direct comparisons of denosumab against pamidronate or clodronate.
- The potential benefits in quality of life associated with SC versus IV administration could not be evaluated in Study 136 due to the double-dummy design.
- It is uncertain if the results of Study 136 are generalizable to patients with poorer health status at the time of initiating treatment.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

January 20, 2016 Meeting
Regrets:

None

Conflicts of Interest:

None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. 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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice 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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