CADTH CANADIAN DRUG EXPERT REVIEW COMMITTEE FINAL RECOMMENDATION

DENOSUMAB

(Xgeva — Amgen Canada)

Indication: Prevention of Skeletal-Related Events due to Bone Metastases From Solid Tumours

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 solid tumours (other than prostate cancer and breast cancer), if the following conditions are met:

Conditions:
- List in a manner similar to intravenous (IV) bisphosphonates.
- Reduced price.

Reasons for the Recommendation:
1. In one double-blind randomized controlled trial (RCT; study 244) enrolling patients with bone metastases from solid tumours (other than prostate and breast cancer but including patients with multiple myeloma), denosumab was non-inferior to zoledronic acid for time-to-first skeletal-related event (SRE; hazard ratio [HR] 0.84; 95% confidence interval [CI] 0.71 to 0.98).
2. A pre-specified analysis excluding patients with multiple myeloma suggested that denosumab is superior to zoledronic acid for reducing the risk of SREs (HR 0.81; 95% CI, 0.68 to 0.96). However, as this was a secondary analysis that is of lower quality than the primary analysis, the results should be interpreted with caution.
3. When considering only current publicly available drug prices at recommended doses and under the assumption that infusion costs are funded by the manufacturer, the annual cost of denosumab (120 mg every 4 weeks; $7,482) is greater than generic zoledronic acid (4 mg/5 mL every 3 to 4 weeks; $2,521 to $3,361), and similar to branded zoledronic acid (Zometa; 4 mg/5 mL every 3 to 4 weeks; $7,203 to $9,604).

Of Note:
- CDEC noted that there may be variability across the individual jurisdictions regarding the most appropriate comparator based on which IV bisphosphonates they fund 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. Denosumab is not indicated for reducing the risk of developing SREs in patients with multiple myeloma. The recommended dose of denosumab is one 120 mg subcutaneous (SC) injection every four weeks.

In response to a request from the CADTH Common Drug Review (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 for reducing the risk of developing SREs in patients with bone metastases from solid tumours (other than breast cancer and prostate cancer).

Summary of CDEC Considerations:
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of denosumab, a summary of pharmacoeconomic information prepared by CDR, and patient group–submitted information about outcomes and issues important to patients with bone metastases from solid tumours.

Patient Input Information
The following is a summary of key information provided by three patient groups, consisting of patients and caregivers that responded to the CDR call for patient input:

- 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 they 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, double-dummy RCT. Study 244 (N = 1,776) evaluated the non-inferiority and superiority of denosumab compared with zoledronic acid based on the first occurrence of an SRE in patients with advanced cancer (excluding breast and prostate cancer) and bone metastases. All patients were strongly recommended to receive concomitant treatment with calcium (≥ 500 mg) and vitamin D (≥ 400 international units [IU]). Patients who had received IV bisphosphonates were excluded, as were patients with a prior history of osteonecrosis of the jaw (ONJ) or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or

any planned invasive dental procedure. The most common primary tumour types were non–small cell lung cancer (40%), multiple myeloma (10%), [redacted]. Denosumab is not indicated for reducing the risk of developing SREs in patients with multiple myeloma.

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 and the degree to which pain interferes with function (pain interference).
- Functional Assessment of Cancer Therapy–General (FACT-G) — a 27-item questionnaire that 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 comprised 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 244 was the time to the first occurrence of an SRE.

Efficacy

- Overall survival and disease progression were similar in the denosumab and zoledronic acid groups; however, mortality was higher with denosumab in the subgroup of patients with multiple myeloma. HRs for denosumab versus zoledronic acid were:
  - Overall survival (full population): 0.95 (95% CI, 0.83 to 1.08)
  - Overall survival (multiple myeloma): 2.26 (95% CI, 1.13 to 4.50)
  - Disease progression: 1.00 (95% CI, 0.89 to 1.12).
- Denosumab was non-inferior, but not superior to zoledronic acid for reducing the risk of a first SRE in patients with advanced cancer and bone metastases. However, when patients with multiple myeloma were excluded from the analysis, denosumab was associated with a significant reduction in the risk of a first SRE compared with zoledronic acid. HRs for denosumab versus zoledronic acid were:
  - Full analysis set (FAS): 0.84 (95% CI, 0.71 to 0.98); $P = 0.0007$ for non-inferiority and $P = 0.0619$ for superiority (adjusted for multiplicity)

  - [redacted]
  - Excluding multiple myeloma: 0.81 (95% CI, 0.68 to 0.96); *P* = 0.0168 for superiority. Statistical tests were not adjusted for multiple analyses.
- [redacted]. 31.4% of patients in the denosumab group and 36.3% of patients in the zoledronic acid group experienced an SRE during the trial.
- There was no statistically significant difference between denosumab and zoledronic acid for time to first-and-subsequent SREs. Rate ratios for denosumab versus zoledronic acid were:
  - FAS: 0.90 (95% CI, 0.77 to 1.04); *P* = 0.1447 for superiority
  - [redacted].
- Denosumab was superior to zoledronic acid for reducing the risk of radiation to bone, the most commonly reported SRE in the study. HRs for the time to first SRE by individual type were:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted].
- [redacted].
- Changes from baseline in analgesic scores, FACT-G, and EQ-5D were low and similar in both the denosumab and zoledronic acid treatment groups; there were no statistical analyses performed for these end points.

Harms (Safety and Tolerability)

- A total of [redacted] of patients in both treatment groups died during Study 244. The most frequently reported causes of death were [redacted].
- At least one serious adverse event was reported for 63% of patients in the denosumab group and 66% of patients in the zoledronic acid group. The most commonly reported serious adverse events were neoplasm progression, dyspnea, pneumonia, respiratory failure, metastases to central nervous system, dehydration, general deterioration, spinal cord compression, pyrexia, anemia, pleural effusion, febrile neutropenia, and vomiting.
- At least one adverse event was reported for 96% of patients in both the denosumab and zoledronic acid groups. The most common adverse events were nausea, anemia, dyspnea, fatigue, constipation, vomiting, back pain, cough, and asthenia. Adverse events associated with renal toxicity were more commonly reported in patients treated with zoledronic acid than in patients receiving denosumab. There were numerically more cases of hypocalcemia in the denosumab group compared with the zoledronic acid group.
- 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. The manufacturer supplied a report that was submitted to the National Institute for Health and Care Excellence (NICE) for

denosumab for the currently assessed indication for review by CDR, though an economic model was not provided for this indication; therefore, an assessment of the cost-effectiveness of denosumab in the Canadian setting was not possible. CDR undertook a review of the published literature and published reviews/recommendations from other health technology assessment agencies for information on the cost-effectiveness of denosumab for this indication.

Based on the CDR Clinical Review report, the data suggests that denosumab (Xgeva) is non-inferior (study 244) to zoledronic acid in reducing the time to a first SRE and at least as effective (indirect comparison) as zoledronic acid in reducing the risk of a first SRE in patients with solid tumours other than prostate cancer or breast cancer. When considering only drug prices, at the current publicly available prices and recommended doses, and assuming that manufacturers pay for infusion costs, the annual cost of denosumab (120 mg every 4 weeks; $7,482) is similar to branded zoledronic acid (Zometa; 4 mg/5mL every 3 to 4 weeks; $7,203 to $9,604 annually) but more expensive than generic zoledronic acid (4 mg/5mL every 3 to 4 weeks; $2,521 to $3,361 annually). In a scenario in which administration costs were assumed not to be borne by manufacturers, denosumab (120 mg every 4 weeks) remained more expensive than generic zoledronic acid (4 mg/5mL every 4 weeks) ($7,513 vs. $5,088 annually).

There is no clinical information for the comparison of denosumab to pamidronate or clodronate. For drug plans that do not list zoledronic acid for reducing the risk of SREs in patients with OST, pamidronate and clodronate may be relevant comparators. Denosumab is more expensive than generic pamidronate (90 mg every 3 to 4 weeks; $1,182 to $1,577 annually), and clodronate (1600 mg to 2400 mg daily; $1,764 to $4,288 annually); but similar to branded pamidronate (90 mg every 3 to 4 weeks; $6,510 to $8,680 annually). In a scenario in which administration costs were assumed to not be borne by manufacturers, denosumab remained more expensive than generic pamidronate dosed every 4 weeks ($7,513 vs. $4,354 annually).

The price of denosumab would need to be reduced to be similar to generic zoledronic acid and generic pamidronate. The extent of the price reduction required will depend on the list prices of comparators (which vary by jurisdiction) and whether manufacturers pay for infusion costs.

Other Discussion Points:
CDEC noted the following:

- The results of an indirect comparison in which the efficacy of denosumab was compared with zoledronic acid or placebo were consistent with the conclusion that denosumab is at least as effective as zoledronic acid and superior to placebo for reducing the risk of a first SRE in patients with bone metastases from solid tumours.
- 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 244 due to the double-dummy design.
- It is uncertain if the results of Study 244 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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