

CDEC FINAL RECOMMENDATION

DENOSUMAB

(Prolia — Amgen Canada)

Indication: Osteoporosis in Men

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that denosumab be listed to increase bone mass in men with osteoporosis who are at a high risk for fracture or who have failed or are intolerant to other available osteoporosis therapy, if the following clinical criteria and condition are met:

Clinical Criteria:

- High fracture risk defined as either: a moderate 10-year fracture risk (10% to 20%) with a prior fragility fracture; or a high 10-year fracture risk ($\geq 20\%$) as defined by either the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool or the World Health Organization's Fracture Risk Assessment (FRAX) tool.
- Contraindication to oral bisphosphonates.

Condition:

- Reduced price.

Reasons for the Recommendation:

1. One double-blind, randomized controlled trial (RCT) (ADAMO; N = 242) conducted in men with low bone mineral density (BMD) demonstrated that denosumab was statistically and clinically superior to placebo for increasing BMD.
2. Denosumab (60 mg every six months; \$716) is more costly than generic zoledronic acid (5 mg/100 mL once per year; \$335) and comparable to branded zoledronic acid (Aclasta; 5 mg/100 mL once per year; \$691). Denosumab is also more costly than oral bisphosphonates with incremental annual costs ranging from \$116 to \$600 per year.

Of Note:

- Contraindications to oral bisphosphonates include renal impairment, hypersensitivity, and abnormalities of the esophagus (e.g., esophageal stricture or achalasia).
- In clinical practice, an unsatisfactory response to bisphosphonates is typically defined as a fragility fracture and/or evidence of a decline in BMD below pre-treatment baseline levels, despite adherence for one year.

Background:

Denosumab has a Health Canada indication to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or in patients who have failed or are intolerant to other available osteoporosis therapy. The recommended dose of denosumab is one 60 mg subcutaneous injection every six months.

Denosumab was previously reviewed by the CADTH Common Drug Review (CDR) for the treatment of post-menopausal women at high risk for osteoporotic fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy ([Notice of CEDAC Final Recommendation](#), March 30, 2011). A notice of compliance (NOC) was issued in November 2012 for the use of denosumab as a treatment to increase bone mass in men with osteoporosis at high risk for fracture.

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 the new 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 this new indication.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of denosumab, two indirect comparisons submitted by the manufacturer, a cost comparison conducted by CDR, and patient group–submitted information about outcomes and issues important to men with osteoporosis.

Patient Input Information

The following is a summary of key information provided by one patient group, consisting of patients and caregivers that responded to the CDR call for patient input:

- Fragility fractures are the main consequence of osteoporosis and their effects can be devastating. Fractures can result in a loss of independence, decreased mobility, isolation, depression and, in some cases, death. In addition to the impact on patients, fractures can have a significant emotional and financial impact on caregivers.
- Bisphosphonates have been the most commonly prescribed medications for men with osteoporosis. Patient groups indicated that some patients are unable to tolerate oral bisphosphonates, particularly because of the gastrointestinal problems with which they are associated, and many of those who can tolerate them find the administration process to be difficult.

Clinical Trials

The CDR systematic review included one placebo-controlled RCT (ADAMO; N = 242) that evaluated the efficacy and safety of denosumab for the treatment of men with low BMD, defined in the trial as a T-score ≤ -2 or a T-score ≤ -1 in patients with a history of major osteoporotic fracture. All patients received concomitant treatment with calcium and vitamin D.

Outcomes

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

- Change from baseline in lumbar spine, hip, and femoral neck BMD.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary efficacy outcome for ADAMO was the mean percentage change in lumbar spine BMD after 12 months of treatment.

Efficacy

- Denosumab was superior to placebo for change from baseline in lumbar spine, hip, and femoral neck BMD after 12 months. The differences between the denosumab and placebo groups were:
 - Lumbar spine: 4.8% (95% confidence interval [CI], 4.0 to 5.6; $P < 0.0001$)
 - Total hip: 2.0% (95% CI, 1.5 to 2.6; $P < 0.0001$)
 - Femoral neck: 2.2% (95% CI, 1.3 to 3.0; $P < 0.0001$).
- Denosumab was associated with a within-group mean percentage change from baseline of 5.7% (95% CI, 5.1 to 6.2) in lumbar spine BMD, which exceeded the estimated minimal clinically important difference of 3%.

Harms (Safety and Tolerability)

- At least one serious adverse event was reported for 9% of patients in the denosumab group and 8% of patients in the placebo group.
- At least one adverse event was reported for 72% and 70% of patients in the denosumab and placebo treatment groups, respectively. The most commonly reported adverse events were back pain, arthralgia, nasopharyngitis, osteoarthritis, myalgia, headache, hypertension, and constipation.
- Withdrawals due to adverse events were reported for 3% and 0% of patients in the denosumab and placebo treatment groups, respectively.
- There were no reports of osteonecrosis of the jaw, atypical femur fractures, fracture healing complications, or hypocalcemia.
- Additional safety data from the open-label extension phase of ADAMO demonstrated a similar frequency and type of adverse events as those observed in the double-blind phase.

Cost and Cost-Effectiveness

As this review was filed by the CDR-participating drug plans, the manufacturer of denosumab was invited to submit economic information but was not willing to do so. The manufacturer provided two indirect comparisons (IDCs) of denosumab and other comparators to support the clinical review but did not include a pharmacoeconomic evaluation for denosumab. As such, the CDR review and CDEC deliberations are limited to cost information that is available in the public domain.

CDR conducted a cost comparison from a public-payer perspective comparing the cost of denosumab to zoledronic acid as treatments to increase bone mass in men with osteoporosis at high risk for fracture, or who have failed or are intolerant to other available osteoporosis therapy. Other comparators considered were oral bisphosphonates — alendronate, alendronate/cholecalciferol, and risedronate — based on their indications for treatments of osteoporosis. Etidronate and clodronate were not considered, as they are not approved for this indication.

Teriparatide was not considered as it is not approved for this indication and was deemed by the clinical expert to be a treatment reserved for severe osteoporosis.

Clinical evidence to support comparing the costs of denosumab with zoledronic acid was based on the IDC provided by the manufacturer, of which the results were consistent in demonstrating that there are no statistically significant differences between the effects of denosumab and zoledronic acid on the change in BMD after 12 months in the hip, femoral neck, and trochanter. Evidence from trials included in the IDC (ADAMO, Boonen, and Study 2308) also suggested that denosumab and zoledronic acid do not have markedly different safety profiles even though harms were not analyzed in the IDC. CDR noted that the IDC did not provide a comparison of denosumab to oral bisphosphonates (i.e., alendronate or risedronate) that, according to the clinical expert, are relevant comparators.

At current publicly available prices and recommended doses, the annual cost of denosumab (60 mg every six months; \$716) is more costly than generic zoledronic acid (5 mg/100 mL once per year; \$335) and comparable to zoledronic acid (Aclasta; 5 mg/100 mL once per year; \$691). Denosumab is more costly than oral bisphosphonates with incremental annual costs ranging from \$116 to \$594: generic alendronate (70 mg weekly or 10 mg daily; \$131 to \$181), generic alendronate/cholecalciferol (70 mg/70 mcg or 70 mg/140 mcg weekly; \$122 to \$182), risedronate (Actonel DR; 35 mg weekly; \$600), and generic risedronate (35 mg weekly; \$130).

Other Discussion Points:

CDEC noted the following:

- Patient groups identified the prevention of fractures as the most important outcome for patients with osteoporosis. The included study evaluated efficacy using change in BMD rather than the incidence of fractures; however, CDEC noted that BMD is a widely used outcome for clinical trials of osteoporosis treatments.
- Current Canadian guidelines for the treatment of osteoporosis focus on fracture risk as opposed to BMD alone. CDEC noted that the available evidence does not specifically evaluate the efficacy of denosumab for improving fracture risk compared with placebo; however, BMD is a significant component of the CAROC and FRAX fracture risk scales that are currently recommended.
- Patient groups indicated that those who are unable to tolerate oral bisphosphonates due to gastrointestinal disorders or problems swallowing expect to see fewer adverse events with denosumab injections, thereby increasing the probability of treatment adherence and effectiveness. There were no reports of gastrointestinal disorders with denosumab throughout the ADAMO trial.
- The manufacturer submitted two IDCs comparing denosumab with zoledronic acid. The results of the IDCs were consistent in suggesting similar efficacy between denosumab and zoledronic acid for changes in BMD; however, due to the small number of studies and between-study heterogeneity, CDEC considered the results of the IDCs to be uncertain.
- Denosumab was previously reviewed by CDR for the treatment of post-menopausal women at high risk for osteoporotic fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy ([Notice of CEDAC Final Recommendation](#), March 30, 2011).
- The product monograph for denosumab states that dose adjustment is not necessary for patients with renal impairment.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no direct comparisons of denosumab against other drugs used for the treatment of osteoporosis in men.
- Patients in the ADAMO trial had not been receiving bisphosphonates (i.e., the first-line treatment for osteoporosis) in the two years prior to enrollment in the study.
- The included study was relatively short-term and did not evaluate the efficacy of treatment with denosumab on the prevention of the fractures.

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 Wijeyesundera.

August 19, 2015 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 pharmaco-economic 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 not 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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