CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

DENOSUMAB
(Prolia — AMGEN Canada Inc.)
Indication: Osteoporosis, Postmenopausal Women

This recommendation supersedes the CADTH Canadian Expert Drug Advisory Committee (CEDAC) recommendation for this drug and indication dated March 30, 2011.

Recommendation
CDEC recommends that denosumab be reimbursed to increase bone mass in postmenopausal women 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:
1. 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 (≥ 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.
2. Contraindication to oral bisphosphonates.

Condition:
At a reduced price.

Reasons for the Recommendation:
Clinical Evidence
Evidence from three published subgroup analyses from one randomized controlled trial (RCT), the FREEDOM study, suggested that the fracture risk reduction associated with denosumab versus placebo was not different between the overall population across all subgroups analyzed, including for high-risk subgroups based on factors such as age >75 years. Therefore, the CADTH Common Drug Review (CDR) could not find any evidence of clinically relevant differences with respect to the benefits of denosumab on fracture risk reduction among women of different age groups. Results from a study by McCloskey et al. suggested that fracture risk assessment using the FRAX tool is an effective means to identify a population of patients who might benefit most from denosumab treatment to reduce the risk of fractures, and supported the conclusion that the use of the CAROC or FRAX tools is more appropriate than individual risk

factors such as age to identify patients who may benefit most from denosumab treatment. The CAROC and FRAX tools are both used in clinical practice in Canada for fracture risk assessment and to identify the need for pharmacological treatment, as per the Osteoporosis Canada 2010 guidelines. Both tools incorporate age, sex, prior fragility fracture, and systemic corticosteroid use, together with bone mineral density (BMD), to define the fracture risk. Based on these tools, patients with a moderate 10-year fracture risk (10% to 20%) or a high fracture risk (> 20% or prior fragility fracture) will benefit from pharmacological treatment.

Economic Evidence
Zoledronic acid is considered to be the most appropriate comparator for denosumab. There is evidence from one open-label, single-centre, RCT and four published relevant indirect comparisons to suggest that there is no statistically significant difference between zoledronic acid and denosumab for treating postmenopausal women with osteoporosis who are at risk for fracture. The evidence that denosumab is at least as effective as zoledronic acid for increasing BMD and reducing the risk of fractures, together with a high degree of uncertainty regarding the true relative effectiveness of denosumab compared with zoledronic acid, supports the criterion of requiring a reduced price for denosumab for treating osteoporosis in women.

Of Note:
1. Contraindications to oral bisphosphonates include renal impairment, hypersensitivity, and abnormalities of the esophagus (e.g., esophageal stricture or achalasia).
2. 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 as treatment to reduce the incidence of fractures in postmenopausal women with osteoporosis who are at high risk for fracture, or who have failed or are intolerant to other available osteoporosis therapy; and as treatment 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.

The CDR-participating drug plans have submitted a request for advice (RFA) to CADTH with respect to alignment of the recommendations issued for the postmenopausal osteoporosis indication in women and the osteoporosis indication in men, particularly with regard to:
- the age criterion (i.e., age >75 years as one of the clinical criteria for women)
- the context in regard to defining bisphosphonate failure
- the usage of the CAROC and FRAX tools in order to evaluate fracture risk.

Submission History:
In 2011, CEDAC recommended that denosumab be listed for women with postmenopausal osteoporosis who would otherwise be eligible for jurisdictional funding for oral bisphosphonates, but for whom bisphosphonates are contraindicated due to hypersensitivity or abnormalities of the esophagus (e.g., esophageal stricture or achalasia). In addition, eligible women were required to meet at least two of the following criteria:
- age >75 years

- a prior fragility fracture
- a BMD T-score ≤ −2.5.

In September 2015, CDEC recommended that denosumab also 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 therapies, with a condition of a reduced price and if the following clinical criteria are met:

- 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 (≥ 20%) as defined by either the CAROC tool or the World Health Organization's FRAX tool.
- Contraindication to oral bisphosphonates.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: updated systematic reviews of RCTs and pivotal studies of denosumab for the postmenopausal osteoporosis indication and the osteoporosis indication for men, cost information, and patient group–submitted information about outcomes and issues important to patients with osteoporosis.

Patient Input Information:

Two patient groups responded to the CDR call for patient input: Osteoporosis Canada and the Arthritis Consumer Experts. Information was obtained from clinical practice guidelines evidence and interviews. The following is a summary of key information provided by the patient groups:

- Fracture assessment tools such as the CAROC or FRAX tools reliably captures patients who are at high risk of fragility fractures. Individual risk factors alone (such as age) might not reflect accurately or adequately a patient's risk of fracture, and are already captured under these tools.
- The listed contraindications of hypersensitivity and esophageal abnormalities of stricture or achalasia are reasonable; however, plans should also take into consideration the patient who simply is intolerant of these bisphosphenates (e.g., as a result of dyspepsia).
- While a fragility fracture after adherence to treatment is an indication of treatment failure, significant loss of BMD should also be considered as such an indication.

Clinical Evidence

Age Criterion

To address the question of whether the two recommendations could be aligned by removing the age criterion for postmenopausal women with osteoporosis, CDR compared the benefits of denosumab in patients of various age groups, including patients older than 75 years of age. CDR identified three relevant published subgroup analyses from one RCT, the FREEDOM study (n = 7,808), evaluating the efficacy and safety of denosumab compared with placebo based on new vertebral fractures after 36 months of treatment in postmenopausal women between 60 and 90 years of age who had a BMD T-score < –2.5 but ≥ –4.0 at lumbar spine or total hip. The results of these subgroup analyses are consistent with the conclusion that there is no evidence of clinically relevant differences with respect to the benefits of denosumab on fracture risk reduction among women of different age groups, supporting the removal of the clinical criterion of age in the recommendation for the reimbursement of denosumab in postmenopausal women

with osteoporosis. Instead, the use of appropriate tools such as CAROC or FRAX, which capture a wide range of risk factors including age, are considered more appropriate to identify patients who may benefit most from denosumab treatment.

Definition of Bisphosphonate Failure and Contraindication
There is evidence to support alignment of the definition of bisphosphonate failure and contraindication in the recommendations for men and women, by updating the 2011 recommendation for women to include renal impairment as a possible contraindication, as well as by including unsatisfactory response to bisphosphonates. Renal impairment is a known contraindication to bisphosphonates in all patients, including women, as documented in the Health Canada product monographs for this drug class. In addition, treatment failure also figures into the Health Canada indication for women.

CAROC and FRAX Tools for Fracture Risk Assessment
There is evidence to support changing the 2011 recommendation for denosumab in women with postmenopausal osteoporosis to align it with the inclusion of reference to the FRAX and CAROC tools that appears in the 2015 recommendation for men. The Osteoporosis Canada 2010 guidelines signified a paradigm shift in the prevention and treatment of osteoporotic fractures, moving the focus from treating low BMD to better identifying the risk of fragility fractures in patients. Two tools are available in Canada for estimating the 10-year risk of a major osteoporotic fracture: the updated CAROC tool; and the World Health Organization's FRAX tool. Both tools incorporate age, sex, prior fragility fracture, and systemic corticosteroid use, together with BMD to define the fracture risk. Based on these tools, patients with a moderate 10-year fracture risk (10% to 20%) or a high fracture risk (> 20% or prior fragility fracture) will benefit from pharmacological treatment. According to the clinical expert consulted by CADTH for this review, the CAROC and FRAX tools are both being used in clinical practice as the gold standard for fracture risk assessment and to identify the need for pharmacological treatment.

Cost and Cost-Effectiveness
At the publicly available price of $357.90 per 60 mg prefilled syringe, the daily cost of denosumab is $1.96 ($716 annually) based on the recommended dose of 60 mg every six months.

In 2011, a cost-utility analysis was submitted by the manufacturer comparing denosumab with alendronate, risedronate, and no treatment in women with postmenopausal osteoporosis. Based on the review by CDR of information provided by the manufacturer at that time, denosumab was not considered cost-effective compared with alendronate, or compared with no treatment in patients unable to take oral bisphosphonates (e.g., alendronate and etidronate). However, when compared with no treatment for patients at high risk of fracture, denosumab was considered to be cost-effective.

Currently, zoledronic acid is considered the most relevant comparator to denosumab as it is reimbursed by some CDR-participating drug plans, which was not the case in 2011 when CDR originally reviewed denosumab. Based on the direct and indirect evidence, denosumab appears to be at least as effective as zoledronic acid for increasing BMD and reducing the risk of fractures, although uncertainty remains regarding relative effectiveness. This supports the use

of a cost analysis, rather than a cost-utility analysis to compare denosumab with zoledronic acid.

At current publicly available prices and recommended doses, the annual cost of treatment with denosumab (60 mg every 6 months; $716) is higher than that of generic zoledronic acid (5 mg/100 mL once yearly; $335) and comparable to that of the branded zoledronic acid product (Aclasta; 5 mg/100 mL once yearly; $691). A 54% reduction in the price of denosumab would be required for cost neutrality with generic zoledronic acid.

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.

April 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 not requested the removal of confidential information.

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