Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**denosumab**
Brand Name	Prolia®
Dosage Form	60 mg/mL solution for injection
Manufacturer	Amgen Canada Inc.
Submission Type	**Ministry Initiated**
Use Reviewed	Secondary prevention of osteoporotic fractures in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min
Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews (CRR)	No, the CRR did not review this indication
Drug Benefit Council (DBC)	The DBC met on February 7, 2022, and March 7, 2022. The DBC considered various inputs including: systematic review prepared by the TI's Drug Assessment Working Group (DAWG): Denosumab for the treatment of patients with documented fragility fracture (secondary prevention) and eGFR < 30 mL/min (severe decrease in kidney function), The 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary, as published in the Canadian Medical Association Journal, Clinical Practice Reviews from two specialists and three family physicians; Patient Input Questionnaire responses from 362 patients, 24 caregivers, and one patient group (Medicines Access Coalition BC); and a Budget Impact Assessment.
Drug Coverage Decision	**No change in Limited Coverage criteria for this patient population**
Date	January 17, 2023
Reasons	**Drug coverage decision is consistent with the DBC recommendation.**

	• There was insufficient evidence from randomised controlled trials to evaluate whether denosumab is effective and safe in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min • There is a potential risk of severe hypocalcemia with serious outcomes, including hospitalization and death, in patients with advanced kidney disease on dialysis treated with denosumab.
Other Information	None

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Canadian Agency for Drugs and Technologies in Health (CADTH) Reimbursement Reviews(CRR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

This document is intended for information only.
It does not take the place of advice from a physician or other qualified health care provider.

Appendix

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Osteoporosis Therapeutic Review

Various Manufacturers

Description:

Current Pharmacare coverage focuses on secondary prevention of osteoporosis-related fractures. Patient groups have approached the Ministry of Health (the Ministry) requesting expansion of bisphosphonate and denosumab coverage in the patient populations described below. Denosumab biosimilars are in development, and while it is unknown when they will become available in Canada, the patent for denosumab (Prolia) will expire on June 25, 2022.

The Ministry has requested the Therapeutics Initiative (TI) to conduct systematic reviews of the currently published literature for each of the questions submitted to the DBC.

The DBC was asked the following questions for consideration:

Based on the evidence provided, what is your recommendation to the British Columbia Ministry of Health (the Ministry) regarding the PharmaCare coverage status of:

1. Oral bisphosphonates (alendronate and risedronate) in patients with no documented fracture (primary prevention), but considered at high risk of having a bone fracture?
2. Denosumab in:

   a. Women with breast cancer, taking aromatase inhibitors without a documented fracture (primary prevention)?
   b. Men with prostate cancer, taking androgen deprivation therapy without a documented fracture (primary prevention)?
3. Denosumab in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min, and a documented fragility fracture (secondary prevention)?

In their review, the DBC considered the following:

- Four systematic reviews prepared by the TI's Drug Assessment Working Group (DAWG): Bisphosphonates for primary prevention of fragility fractures in men and women (Final Version, December 14, 2021); Denosumab for the treatment of patients with breast cancer without metastasis who are on aromatase inhibitors (Final Version, December 17, 2021); Denosumab for the treatment of patients with prostate cancer without metastasis who are on androgen deprivation therapy (Final Version, December 17, 2021); and Denosumab for the treatment of patients with documented fragility fracture (secondary prevention) and eGFR < 30 mL/min (severe decrease in kidney function) (Final Version, August 23, 2021).
- A supplemental pharmacoeconomic report prepared February 9, 2022 by Adam Raymakers and Dean Regier, following the first DBC meeting titled "Current evidence for the use of denosumab as primary prevention for fractures in patients receiving AIs as treatment for breast cancer"
- The 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary, as published in the Canadian Medical Association Journal (CMAJ November 23, 2010, 182(17) DOI:10.1503/cmaj.100771).
- Clinical Practice Reviews from two specialists and three family physicians; Patient Input Questionnaire responses from 362 patients, 24 caregivers, and one patient group (Medicines Access Coalition BC); and a Budget Impact Assessment.

Dosage Forms:

Bisphosphonates

Alendronate (Fosamax, generics)

Alendronate/cholecalciferol (Fosavance, generics)

Risedronate (Actonel, generics)

RANK ligand inhibitor

Denosumab (Prolia)

Recommendations:

1. **The DBC recommends that the BC Ministry of Health (the Ministry) not include alendronate or risedronate as a benefit on the BC PharmaCare formulary for the primary prevention of osteoporotic fractures, regardless of the patient's risk of fracture.**
   - Reasons: in men, there are no primary prevention trials of alendronate and risedronate, two oral bisphosphonates in use in BC. One primary prevention randomized controlled trial (RCT) in men of annual treatment with the intravenous bisphosphonate zoledronic acid was underpowered to identify a change in clinical fractures.
   - No new RCTs on this topic are in progress, and the 10-year lag in increased fracture rates in men vs women suggests that lower fracture prevalence would require large trials to detect the small differences.
   - The Cochrane protocol on bisphosphonate use in men was withdrawn in 2019 (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011074.pub2/information#versionTable).
   - In women, several RCTs identified as primary prevention trials by the Agency for Healthcare Research and Quality (AHRQ) in older women were found to have higher rates of "silent" radiographically detected vertebral fractures than the Cochrane review threshold definition of < 20%.
   - For alendronate, AHRQ included 3 RCTs that reported "no fracture at baseline" (Chesnut 1995; Cummings 1998; Ascott-Evans 2003).
   - For risedronate, 1 RCT with "no fracture at baseline" met AHRQ inclusion criteria (Mortensen 1998), which reported no clinical relevance to fracture findings.
   - RCT evidence does not support the use of alendronate or risedronate for primary prevention in older adult women with no documented fracture. No RCT was identified that enrolled postmenopausal women on the basis of a 'high risk' score in the absence of documented fractures.
   - RCTs evaluating community screening strategies using a combination of case finding and treatment strategies did not find a difference in clinical fractures.
   - Bisphosphonates are associated with harms, including the potential for serious thigh bone fractures and osteonecrosis. Health Canada has published a number of post market warnings and safety reviews on oral bisphosphonates, including an advisory about a "possible risk of rare but serious thigh bone fracture" with bisphosphonates in October 2010, which was updated in December 2012 to confirm a "small but increased risk of unusual fractures of thigh bone." The risk of "Atypical Subtrochanteric and Diaphyseal Femoral Fractures" is now included in the product monographs.
   - A 2016 Health Canada Summary Safety Review of oral and injectable bisphosphonates (alendronate, clodronate, etidronate, pamidronate, risedronate and zoledronate) confirmed the known risk of jaw bone loss with bisphosphonate product use, and further concluded "this risk is higher with intravenous bisphosphonate products, especially in cancer patients" (https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00137&wbdisable=false).
   - A 2017 Health Canada review examining the risk of severe bone damage (osteonecrosis) beyond the area of the jaw bone noted the product monographs for alendronate, zoledronic acid and clodronate already contain warnings about the risk of severe bone damage of the outer ear canal but did not find evidence to extend this warning to other bisphosphonates (https://www.canada.ca/en/health-canada/services/drugs-health-

products/medeffect-canada/safety-reviews/summary-safety-review-bisphosphonates-assessing-potential-risk-severe-bone.html).

2. **a) The DBC recommends that the Ministry add denosumab to the BC PharmaCare formulary for primary prevention of osteoporotic fractures in women with breast cancer who are receiving aromatase inhibitor therapy, if a price reduction is achieved.**
   - Clinical evidence suggests that denosumab may be an effective treatment for reducing clinical fractures in patients undergoing treatment for breast cancer with aromatase inhibitors.
   - In two RCTs (Gnant 2015, Ellis 2008) in 3672 patients, non-vertebral fractures were significantly decreased with denosumab vs placebo.
   - Denosumab for primary prevention of clinical fractures significantly reduced clinical fractures, vertebral fractures and non-vertebral fractures as compared to placebo. There are no head-to-head trials with bisphosphonates.
   - RCTs showed no significant increase in serious harm with denosumab compared to placebo, but a higher incidence of known adverse events (e.g., hypocalcemia, back pain and arthralgia).
   - The duration of treatment with denosumab is unknown, and rapid bone loss occurs after discontinuation.
   - There were no cost-effectiveness studies identified in the public domain. Since the cost-effectiveness of denosumab in the primary prevention setting will depend on cost, and because the patent of denosumab will be expiring in 2022, the Ministry should consider a price reduction.
   - For women with early breast cancer, a Cochrane review (O'Carrigan 2017) found that bisphosphonates did not significantly reduce the incidence of fractures when compared to placebo/no bisphosphonates, although there were numerous limitations with this data.

2. **b) The DBC recommends that the Ministry not include denosumab on the BC PharmaCare Formulary for primary prevention of osteoporotic fractures in men with prostate cancer receiving androgen deprivation therapy.**
   - Reasons: the TI systematic review found two RCTs that met the inclusion criteria (Smith 2009, Yoshida 2020). In the RCTs, denosumab did not significantly differ from placebo in total number of clinical fractures.
   - Denosumab reduced the incidence of radiographically defined vertebral fractures compared to placebo but the proportion of symptomatic or asymptomatic vertebral fractures was not reported.
   - There was no significant increase in harm with denosumab versus placebo.
   - There is insufficient scientifically valid evidence to determine the relative efficacy of denosumab versus active comparators.

3. **The DBC recommends that the Ministry not include denosumab on the BC PharmaCare formulary for secondary prevention of osteoporotic fractures in patients with an estimated glomerular filtration rate of less than 30 mL/min.**
   - Reasons: one post hoc subgroup analysis of a double-blind, placebo controlled, parallel-group RCT (FREEDOM) was identified to support this indication.
   - There are many limitations for using the results of the FREEDOM trial for this indication, as bisphosphonates cannot be used in this renal population. As well: patients with chronic kidney disease were excluded, therefore the number of patients with eGFR < 30 mL/min was only 73 and valid analysis was not possible; the criteria for determining vertebral fracture was unnecessarily vague and the clinical relevance of morphometric vertebral fracture is questionable when in some case series 70% have been found to not be clinically relevant; insufficient information was provided to evaluate the comparability of study groups; data on adverse events were

unblinded; and the duration of 36 months was relatively short after which the placebo arm was discontinued in favor of an extension study.
- As a result, there is insufficient evidence from RCTs to evaluate whether denosumab has a therapeutic advantage in patients with severe CKD, eGFR < 30 mL/min (stage 4) and < 15 mL/min chronic kidney failure.

Other Considerations

- The DBC considered an internal Budget Impact Assessment, which indicated that PharmaCare would incur a significant budget impact for expanding the Limited Coverage criteria for oral bisphosphonates to include primary prevention (i.e., patients with no documented fracture), and would also incur a significant budget impact for expanding the criteria for denosumab to include primary prevention in women with breast cancer and men with prostate cancer and secondary prevention in patients with an eGFR < 30 mL/min.
- Extensive patient, caregiver and patient group input indicated that patients with osteoporosis commonly experienced chronic pain, limited activities, and worries about their risk of injury. Some patients reported experiencing multiple fractures, and many patients reported loss of height and change in posture. The patient group noted the potential for death or institutionalization resulting from osteoporosis-related fractures.
- Approximately half of the patients had tried a bisphosphonate, and of those, approximately one quarter thought their treatment was successful. Many patients discontinued treatment due to adverse events, primarily gastrointestinal problems such as reflux.
- Of the patients who had tried denosumab, 50% reported increased bone density. Patients reported that denosumab was better tolerated, although some noted they experienced joint pain and gastrointestinal problems. The cost and ability to access denosumab treatment were the main concerns that patients identified.