Common Drug Review
Request for Advice

October 2016

Drug	Denosumab (Prolia)
Indication	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. Treatment to reduce the incidence of fractures in postmenopausal women with osteoporosis at high risk for fracture; or who have failed or are intolerant to other available osteoporosis therapy.
Manufacturer	Amgen Canada Inc.
Request for Advice Questions	The CADTH Common Drug Review (CDR)-participating drug plans are requesting advice with respect to the alignment of the recommendations issued for the postmenopausal osteoporosis indication in women with the osteoporosis indication in men, particularly with regard to: • the age criterion for women • the context in regard to defining bisphosphonate failure; and • the usage of the CAROC and FRAX tools for fracture risk assessment.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in rheumatology who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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TABLE OF CONTENTS

ABBREVIATIONS

AE	adverse event
BMD	bone mineral density
CAROC	Canadian Association of Radiologists and Osteoporosis Canada
CEDAC	Canadian Expert Drug Advisory Committee
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
CI	confidence interval
DB	double blind
FRAX	the World Health Organization's Fracture Risk Assessment
IDC	indirect comparison
QALY	quality-adjusted life-year
RCT	randomized controlled trial

1. BACKGROUND

1.1 Postmenopausal Women with Osteoporosis

The recommendation made for denosumab in 2011 by the Canadian Expert Drug Advisory Committee (CEDAC) regarding postmenopausal women with osteoporosis is presented the table that follows.

Recommendation
CEDAC recommended in 2011 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), and have at least two of the following: • age >75 years • a prior fragility fracture • a bone mineral density (BMD) T-score ≤ -2.5.
Reason(s) for Recommendation
In one double-blind randomized controlled trial comparing denosumab with placebo in postmenopausal women with low BMD T-scores, denosumab achieved a statistically significantly greater reduction in the incidence of new vertebral and hip fractures, in both the total patient population and a predefined high-risk subgroup. A cost-utility analysis based on the high risk subgroup resulted in a cost per quality-adjusted life-year (QALY) of $29,000 for denosumab compared with no treatment. The cost per QALY was higher when the total patient population was considered.

The primary conclusions in the 2011 CDR clinical review were as follows.

> *In postmenopausal women with low BMD, FREEDOM demonstrated that compared with placebo, denosumab significantly reduced the risk of new vertebral, non-vertebral, and hip fractures and increased BMD relative to baseline. Other trials showed that denosumab was both non-inferior and statistically superior to alendronate in terms of increases in total hip BMD. There was some evidence that denosumab is associated with better treatment adherence and higher satisfaction over alendronate administered weekly. There were insufficient data to determine the comparative efficacy of denosumab and other anti-osteoporosis medications in terms of fracture risk. With the exception of cellulitis requiring hospitalization, the safety of denosumab appeared to be similar to that of placebo or active comparators in the included [randomized controlled trials] RCTs. Preliminary results from the FREEDOM open-label extension study suggest denosumab continues to be safe and well tolerated for up to five years of continuous treatment, although further long-term data are required to characterize the safety profile with greater certainty.*
>
> *In Canada, denosumab is indicated for the treatment of postmenopausal women at high-risk for osteoporotic fracture (i.e., history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant of other available osteoporosis therapy. Currently, BMD is considered to be one risk factor for fracture among many, the most important of which is prior fracture. The goals of therapy in osteoporosis are to prevent fragility fractures among those at high-risk, not to simply increase BMD. However, the trials identified in this review have important limitations in terms of their applicability to these populations. All of the included clinical trials enrolled patients solely on BMD T-scores and not fracture risk as it is currently defined. Although included patients had a wide range of fracture risks at baseline, only the FREEDOM trial provided evidence that the benefit of denosumab (versus placebo) was similar across fracture risk profiles, including a subgroup at high risk of fracture. No such data are available from the direct comparisons with alendronate. Based on its mechanism of action and the safety data available to date, denosumab may be tolerated by some patients who have contraindications to, or are intolerant of, bisphosphonates, although there are no specific data available for this population. There are also no data regarding the efficacy and safety of denosumab in patients who have failed other anti-osteoporosis medications.*

1.2 Men with Osteoporosis

The recommendation made by Canadian Drug Expert Committee (CDEC) in 2015 regarding denosumab in men with osteoporosis is presented below.

Recommendation
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 (≥ 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.
Reason(s) for Recommendation
• One double-blind, RCT (ADAMO; N = 242) conducted in men with low BMD demonstrated that denosumab was statistically and clinically superior to placebo for increasing BMD. • 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.

The primary conclusions for the 2015 CDR clinical review were as follows.

> *The results of the ADAMO study demonstrated the superiority of denosumab over placebo for improving lumbar spine BMD after 12 months of treatment in men with low BMD. In the open-label extension phase, denosumab continued to be effective in improving BMD up to 24 months. However, the trial did not provide evidence to inform on the effects of denosumab on clinical outcomes such as fractures and quality of life. There were no reports of osteonecrosis of the jaw, atypical femur fractures, fracture healing complications, or hypocalcemia. Few patients experienced dermatologic [adverse events] (AEs) or malignancies, and similar proportions of patients developed infections in both treatment groups. The generalizability of the results of ADAMO are limited by the fact that the trial population had a slightly lower risk of fracture than that seen in clinical practice, as well as by the exclusion of patients with commonly seen comorbid conditions, and by the exclusion of patients who had received recent bisphosphonate treatment. The results of two indirect comparisons submitted by the manufacturer in which the efficacy of denosumab was compared to zoledronic acid were consistent with the conclusion that denosumab is at least as effective as zoledronic acid for increasing BMD in men with osteoporosis.*

2. REQUEST FOR ADVICE

2.1 Background

The CDR-participating drug plans have submitted a request for advice (RFA) to CADTH regarding the 2011 and 2015 recommendations for denosumab (Prolia) in osteoporosis. 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 therapy, 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.

2.2 RFA Questions

The CDR-participating drug plans have requested advice with respect to alignment of the recommendations issued for the postmenopausal osteoporosis indication in women with 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.

3. CDR APPROACH TO THE REQUEST FOR ADVICE

In order to address the RFA questions, the CDR review team updated the systematic review in the clinical report for the postmenopausal osteoporosis indication to include clinical data published since the original review in 2011, and similarly updated the review for the indication in men from September 2015, with the objective of identifying any new clinical data. RCTs were selected for inclusion based on the selection criteria defined and presented in the protocols in the original clinical reports. In addition, relevant published indirect comparisons of denosumab versus zoledronic acid were also selected for inclusion. The detailed review methodology is presented in APPENDIX 1: METHODOLOGY.

The CDR review team also identified and present, in the following section, recommendations from the major clinical guidelines applicable to Canada. A clinical expert in osteoporosis was included in the review team to provide input on the interpretation of findings.

4. CLINICAL FINDINGS

4.1 Age Criterion

The recommendation for osteoporosis in men in 2015 referred to the FRAX or CAROC tools to define men at a high risk of fracture, which was a criterion required for reimbursement. By contrast, the 2011 recommendation for postmenopausal women with osteoporosis based high fracture risk assessment on a combination of individual risk factors, including an age criterion that women be older than 75 years. The specification of an age-based criterion is therefore discordant between the two recommendations.

To address the question of whether the two recommendations could be aligned by removing the age criterion for postmenopausal women with osteoporosis, evidence is needed to compare the benefits of denosumab in patients of various age groups, including patients older than 75 years of age.

From the literature search, CDR identified three relevant published subgroup analyses from one RCT, the FREEDOM study. FREEDOM (n = 7,808)[1] evaluated 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 and a BMD T-score < –2.5 but ≥ -4.0 at lumbar spine or total hip. Details of the FREEDOM trial and three subgroup analyses are presented in Table 1.

TABLE 1: SUMMARY OF FREEDOM TRIAL AGE-BASED SUBGROUP ANALYSES

	FREEDOM[1] (Overall)	Palacios et al. 2015[2]	McClung et al. 2012[3]	Boonen et al. 2011[4]
DESIGNS	International, multicenter, DB RCT evaluating the efficacy and safety of denosumab versus placebo. Duration of 36 months. N = 7,808 patients.	Post-hoc subgroup analysis.	Subgroup analyses prospectively planned before study unblinding.	Post-hoc subgroup analyses of women at higher risk for fractures.
POPULATIONS	• Postmenopausal women between 60 and 90 years. • Lumbar spine or total hip BMD T-score < –2.5 but ≥ –4.0. • 45% of patients with a prior fragility fracture.	Fragility fracture efficacy evaluated based on baseline age (≥ 75 years and < 75 years), in patients with and without prevalent fracture.	Age: ≥ 75 years and < 75 years.	Women aged ≥ 75 years. For the outcome of hip fractures only.
MAIN OUTCOME RESULTS	The incidence of new vertebral fracture was 2.3% in the denosumab group and 7.2% in the placebo group (RR: 0.32, 95% CI, 0.26 to – 0.41; *P* <0.0001). Denosumab also reduced the risk of non-vertebral fractures (RR: 0.80 [0.67, 0.95]; *P* = 0.0106) and hip fractures (RR: 0.60 [0.37 to 0.97]; *P* = 0.0362).	Incidence of fracture in the overall population: RRR: 40%; *P* < 0.0001 Patients with prior fracture < 75 years: RRR: 41%; *P* < 0.0001 ≥ 75 years: RRR: 37%; *P* = 0.0004 Patients without prior fracture < 75 years: RRR: 44%; *P* < 0.0001 ≥ 75 years: RRR: 32%; *P* = 0.0492	Risk ratio (95% CI) Vertebral fractures ≥ 75 years: 0.30 (0.22 to – 0.41) < 75 years: 0.36 (0.25 to – 0.53) Interaction p value: *P* = 0.2909 Non-vertebral fractures ≥ 75 years: 0.78 (0.63 to 0.96) < 75 years: 0.84 (0.63 to 1.12) Interaction *P* value: *P* = 0.0134	Hip fractures in patients ≥ 75 years: 2.3% placebo *vs.* 0.9% denosumab; *P* < 0.01.
AUTHORS CONCLUSIONS	FREEDOM demonstrated that compared with placebo, denosumab significantly reduced the risk of new vertebral, non-vertebral, and hip fractures and increased BMD relative to baseline.	Denosumab reduced the risk of fragility fractures, including secondary fragility fractures, to a similar degree in all risk subgroups examined, regardless of age.	Denosumab reduced the risk of new vertebral fractures to a similar degree in all subgroups. The effect of denosumab on non-vertebral fractures was similar in patients older or younger than 75 years.	Denosumab significantly reduced the risk of hip fractures in patients ≥ 75 years. No significant treatment-by-subgroup interaction was demonstrated based on any higher-risk subgroups investigated.

BMD = bone mineral density; DB = double blind; CI = confidence interval; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction.

Results from the analyses of the FREEDOM data presented in Palacios et al. 2015,[2] McClung et al. 2012,[3] and Boonen et al. 2011[4] suggest 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 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.

Palacios et al.,[2] McClung et al.,[3] and Boonen et al.[4] used individual risk factors to assess fracture risk and obtained consistent results across subgroups of patients with various risk factors. However, results from another publication[5] identified in the literature search suggest 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. Indeed, McCloskey[5] used the FRAX tool to assess fracture risk among women in the FREEDOM trial population. McCloskey[5] reported that the magnitude of the risk reduction observed with denosumab versus placebo was greater in higher-risk patients. These results indicate that the use of appropriate tools such as CAROC or FRAX are more appropriate than individual risk factors such as age to identify patients who may benefit most from denosumab treatment.

The clinical expert consulted by CADTH for this review indicated that in clinical practice, the use of the CAROC or FRAX tools is considered to be the most appropriate approach to assessing fracture risk. Although individual risk factors such as age have a significant impact on fracture risk, the CAROC and FRAX tools capture a wide range of risk factors (including age) and therefore, they can predict fracture risk more accurately. Additional details regarding the use of these tools are presented under Section 4.3.

The evidence presented above supports the removal of the clinical criterion of age in the recommendation for the reimbursement of denosumab in postmenopausal women with osteoporosis. Instead of defining the high-risk population of women based on age >75 years, presence of a prior fragility fracture, and a BMD T-score ≤ −2.5, it would be more appropriate to define "high risk" in women as it has been defined for men, as follows:

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.

4.2 Definition of Bisphosphonate Failure and Contraindication

CDEC recommended that denosumab be listed to increase bone mass in men with osteoporosis who have failed or are intolerant to other available osteoporosis therapy, and noted that contraindications to oral bisphosphonates include renal impairment, hypersensitivity, and abnormalities of the esophagus; and 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. The aforementioned recommendation was aligned with regard to treatment failure to the Health Canada indication for denosumab in men. Indeed, Health Canada has indicated denosumab as a "treatment to increase bone mass in men with osteoporosis at high risk for fracture […] *or in patients who have failed or are intolerant to other available osteoporosis therapy"* [emphasis added by CADTH].[6] The definition for unsatisfactory response to bisphosphonates used in the CDEC recommendation was based on the experience of clinical specialists in Canada. Note that contraindications to oral bisphosphonates in the CDEC recommendation for men as well as in the product monograph for bisphosphonates are not limited to abnormalities of the esophagus, but also include renal impairment and hypersensitivity. By

contrast, the 2011 CEDAC recommendation for women with postmenopausal osteoporosis stated that denosumab be listed in women with postmenopausal osteoporosis for whom bisphosphonates are contraindicated due to hypersensitivity or abnormalities of the esophagus. This is discordant with the 2015 recommendation for men with osteoporosis.

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 in the Health Canada indication for women, as denosumab is indicated for the treatment of postmenopausal women with osteoporosis at high risk for 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*" [emphasis added by CADTH].[6] Based on this evidence, the definition of bisphosphonate failure and contraindication in the recommendations for men and women could be aligned by updating the 2011 recommendation for women to include renal impairment as a possible contraindication, as well as including unsatisfactory response to bisphosphonates.

4.3 CAROC and FRAX Tools for Fracture Risk Assessment

The CDEC recommendation for denosumab in men with osteoporosis defined a high risk of fracture as a moderate 10-year fracture risk (10% to 20%) with a prior fragility fracture or a high 10-year fracture risk (≥ 20%); both as defined by either the CAROC or FRAX tool. This definition of fracture risk was based on clinical guidelines and risk fracture definitions used in clinical practice at the time the recommendation was issued in 2015. 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.[7] Two tools are available in Canada for estimating the 10-year risk of a major osteoporotic fracture:[7]

- the updated tool of the CAROC
- the FRAX tool of the World Health Organization.

Both tools incorporate age, sex, prior fragility fracture, and systemic corticosteroid use, together with BMD to define the fracture risk.[7] 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.[7]

In contrast to the 2015 recommendation for men, the definition used to identify patients with a high fracture risk in the 2011 recommendation for women with postmenopausal osteoporosis was based on three specific factors: age, fracture history, and BMD (see above). Therefore, the 2011 recommendation did not rely on validated risk assessment tools such as the FRAX and CAROC to define fracture risk, and is thus discordant with the 2015 recommendation for men.

The clinical expert consulted by CADTH for this review highlighted the importance of appropriate fracture risk assessment in order to correctly identify patients who will benefit from a pharmacological drug, in addition to preventing inappropriate treatment of other patients (i.e., those patients with a lower fracture risk). 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, as per the Osteoporosis Canada 2010 guidelines. Therefore, 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.

5. COST INFORMATION

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 CDR review of information provided by the manufacturer, 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. For the review in 2015 of denosumab for osteoporosis in men, a cost comparison that was conducted to compare denosumab, zoledronic acid, and oral bisphosphonates as the available evidence indicated similar efficacy and safety between the comparators. This reflected the fact that at the time of the 2015 review, zoledronic acid was reimbursed by some CDR-participating drug plans, which was not the case in 2011 when denosumab was reviewed for postmenopausal osteoporosis. Results of the cost comparison in 2015 showed denosumab to be more expensive than oral bisphosphonates and generic zoledronic acid, but similar in cost to the branded form of zoledronic acid (Aclasta). The average cost of using denosumab and zoledronic acid to treat osteoporosis, as calculated by CADTH, is presented in the table below. For a complete summary of the costs of all relevant comparators, see APPENDIX 5: COST TABLE.

Drug / Comparator	Strength	Dosage Form	Price ($)	Average Use	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Denosumab (Prolia)	60 mg	Prefilled syringe	357.9000	60 mg every 6 months	1.96	716
Zoledronic acid (Aclasta, generics)	5 mg/ 100 mL	Infusion	335.4000 690.9200	Once yearly	0.92 1.89	335 691

Source: Ontario Drug Benefit (effective January 2016) prices unless otherwise stated.

Because denosumab was determined in the 2015 economic analysis to be more expensive than generic zoledronic acid, as well as oral bisphosphonates, the 2015 CDEC recommendation for denosumab for the treatment of osteoporosis in men included the condition of a reduced price, but not necessarily below that of generic zoledronic acid. This is discordant with the 2011 recommendation for postmenopausal osteoporosis, which did not stipulate this condition.

In the CADTH review of osteoporosis in men in 2015, zoledronic acid was considered to be the most appropriate comparator. The comparison between denosumab and oral bisphosphonates was deemed less relevant than the comparison between denosumab and zoledronic acid, because oral bisphosphonates are considered to be first-line treatment options, whereas the injectable agents denosumab (subcutaneous injection) and zoledronic acid (intravenous infusion) are more often considered second-line options according to input received from clinical experts. To help address the discrepancy between the 2011 and 2015 recommendations with respect to the condition of a reduced price, the review team assessed whether there was any evidence to compare denosumab to zoledronic acid in a population of postmenopausal women at high risk for fracture. If, as in the case of men, denosumab and zoledronic acid were found to have similar clinical efficacy in treating osteoporosis in women, then the condition of a reduced price could apply to the recommendation for women; thereby, bringing that aspect of the recommendations for men and women into alignment.

Accordingly, the CDR review carried out a literature search for relevant evidence and identified one open-label, single-centre RCT in which denosumab was compared directly with zoledronic acid for treating women with osteoporosis.[8] Specifically, Anastasilakis et al. 2015[8] evaluated the efficacy of denosumab compared with zoledronic acid based on lumbar spine BMD after 12 months of treatment in postmenopausal women with low bone mass (defined as a T-score ≤ –2) who were previously treated with zoledronic acid for 1 year. Several limitations are associated with the small sample size of the trial (n = 58), and generalizability of the Greek population included in the study to Canadian patients. In addition, the trial population was not considered at high risk of fractures, considering the inclusion of patients with a T-score ≤ –2 and the fact that 93% of patients had no previous fracture. In the presence of adequate statistical power, the results of the study suggested that there was no statistically significant difference between the two interventions, as denosumab achieved similar increases compared with zoledronic acid in lumbar spine BMD after 12 months compared with baseline (4.5% with denosumab and 4.4% with zoledronic acid; *P* = 0.560).

In addition to the aforementioned RCT, a total of four published relevant indirect comparisons (IDCs) were retrieved from the literature. Details of each IDC are presented in Table 2. The IDCs in Table 2 had several limitations, including heterogeneous populations, which means that there is some uncertainty regarding their conclusions. However, despite these limitations, the results of these IDCs were consistent with the conclusion that there is no evidence of clinically relevant differences with respect to fracture risk reduction associated with denosumab compared with zoledronic acid treatment in postmenopausal women with osteoporosis at risk for fracture.

The manufacturer of denosumab provided additional evidence from several studies to suggest that denosumab might be superior efficacy to zoledronic acid. Most studies, however, were of relatively low quality (based on CADTH quality standards). However, the manufacturer did provide evidence in the form of one double-blind, multicenter RCT in which denosumab was compared directly to zoledronic acid in women with osteoporosis previously treated with oral bisphosphonates.[9] Specifically, Miller 2015 (n = 643)[9] evaluated the efficacy of denosumab compared with zoledronic acid based on lumbar spine BMD after 12 months of treatment in postmenopausal women aged ≥ 55 years with a T-score ≤ –2.5 who were previously treated with oral bisphosphonates for at least two years. The results of the study suggested that denosumab was associated with a statistically significant change in lumbar spine BMD after 12 months compared with baseline (3.2% with denosumab versus 1.1% with zoledronic acid; *P* <0.0001). However, a major limitation of this study is the fact that these results have only been reported as a meeting abstract. Therefore, details regarding important aspects of the study, including the patient population, trial quality, methodology, and detailed outcome data, are not available for critical appraisal. Consequently, these results must be viewed as uncertain in light of these limitations.

Based on the information presented above, the majority of the evidence available is consistent with the conclusion that denosumab is at least as effective as zoledronic acid for increasing BMD and reducing the risk of fractures. This conclusion, together with the high degree of uncertainty regarding the true relative effectiveness of denosumab compared with zoledronic acid, supports alignment of the recommendation for postmenopausal women with the recommendation for men with respect to the criterion of requiring a reduced price for denosumab.

TABLE 2: SUMMARY OF INDIRECT COMPARISONS OF DENOSUMAB VERSUS ZOLEDRONIC ACID

	Migliore 2013[10]	Freemantle 2013[11]	Murad 2012[12]	Hopkins 2011[13]
Study design / Statistical methods	Mixed treatment comparisons based on the Markov Chain Monte Carlo methods.	Adjusted indirect comparisons using an adapter version of the Bucher approach; and mixed treatment comparisons using a Bayesian approach.	Random effects network meta-analysis using Markov Chain Monte Carlo methods.	Bayesian indirect treatment comparison using Markov Chain Monte Carlo methods.
Included Population(s)	Postmenopausal women with osteoporosis only.	Postmenopausal women with osteoporosis only.	Men and Women at risk of fragility fractures (including osteopenia).	Postmenopausal women with osteoporosis only.
Interventions	Alendronate, risedronate, ibandronate, **zoledronic acid, denosumab**	**Denosumab,** alendronate, risedronate, ibandronate, **zoledronic acid,** etidronate, strontium ranelate, teriparatide, raloxifene	Bisphosphonates (including **zoledronic acid**), teriparatide, selective estrogen receptor modulators, **denosumab,** calcium and vitamin D	Alendronate, **denosumab,** etidronate, ibandronate, raloxifene, risedronate, strontium, teriparatide, **zoledronic acid**
Primary Outcome	Vertebral fractures	Fracture risk	Fracture risk	Fracture risk
Included Studies (Denosumab and zoledronic acid)	Black 2007 (zoledronic acid) Lyles 2007 (zoledronic acid) Cummings 2009 (denosumab)	Black 2007 (zoledronic acid) Brown 2009 (denosumab) Cummings 2009 (denosumab)	Black 2007 (zoledronic acid, women) Bone 2008 (denosumab, women) Brown 2009 (denosumab, women) Chapman 2009 (zoledronic acid, mixed) Cummings 2009 (denosumab, women) Ellis 2008 (denosumab, women) Grey 2009 (zoledronic acid, women) Lyles 2007 (zoledronic acid, mixed) McClung 2006 (denosumab, women) Reid 2002 (zoledronic acid, women) Smith 2009 (denosumab, men)	Black 2007 (zoledronic acid) Cummings 2009 (denosumab)
Main Results (Denosumab versus zoledronic acid only)	Zoledronate had the highest probability (52%) of being most effective versus placebo, followed by denosumab (46% probability). OR (95% CI), = 1.01 (0.71 to 1.38)	New vertebral fractures: RR = 1.08 (95% CI, 0.78 to 1.51) Non-vertebral fractures: RR = 1.08 (95% CI, 0.87 to 1.35) Hip fractures: RR = 1.03 (95% CI, 0.57 to 1.86)	Vertebral fractures: OR = 1.03 (95% CrI, 0.52 to 2.08) Non-vertebral fractures: OR = 0.93 (95% CrI, 0.70 to 1.27) Hip fractures: OR = 1.02 (95% CrI, 0.54 to 1.93)	Vertebral fractures: OR = 1.16 (95% CrI, 0.66 to 1.88) Non-vertebral fractures: OR = 1.08 (95% CrI, 0.73 to 1.62) Hip fractures: OR = 1.36 (95% CrI, 0.30 to 3.48)
Relevant Conclusions	The mixed treatment comparisons did not show a statistically significant difference among any of the interventions.	Results are consistent with the conclusion that there is no statistically significant difference between these two interventions.	Results are consistent with the conclusion that there is no statistically significant difference between these two interventions.	Zoledronic acid and denosumab have high probabilities of being among the most efficacious options for non-vertebral and vertebral fractures, but there were no statistically significant differences between them.

CI = confidence interval; CrI = credible interval; OR = odds ratio; RR = relative risk.

6. OTHER CONSIDERATIONS

Experience from specialists' clinical practice suggests that convenience of administration is a major factor in selecting osteoporosis treatment. The fact that denosumab is administered subcutaneously, compared with zoledronic acid that needs to be administered intravenously, provides additional benefits in terms of accessibility, convenience, and tolerance for osteoporosis patients. The availability of an option with a subcutaneous route of medication delivery often eliminates the need for a visit to a facility for administration and is a communicated advantage in terms of quality of life, in addition to reducing the burden on the health care system. Denosumab also presents with the advantage that no dose adjustment is necessary in patients with renal impairment, while bisphosphonates such as zoledronic acid are associated with an increased risk of clinically significant deterioration in renal function.

According to the patient input received by CADTH, there is a consensus that the use of fracture assessment tools such as the CAROC or FRAX tools reliably captures patients who are at high risk of fragility fractures. The use of individual risk factors such as age and BMD alone might not reflect accurately a patient risk of fracture, and are already captured under the CAROC and FRAX tools. The patient input submitted to CADTH highlighted that while the listed contraindications of hypersensitivity and esophageal abnormalities of stricture or achalasia are reasonable, it should also take into consideration the patient who simply is intolerant of these drugs (i.e., dyspepsia). Many persons with dyspepsia sufficient to prevent the use of bisphosphonates would not demonstrate either stricture or achalasia at endoscopic and/or radiologic evaluation of the esophagus, and therefore, would be denied reimbursement for denosumab according to the present recommendation.

7. CONCLUSIONS

A review of new clinical evidence and discussion with clinical experts revealed evidence to support the request from the CDR-participating drug plans to align the 2011 recommendation for denosumab in women with postmenopausal osteoporosis with the 2015 recommendation made for men with osteoporosis. Specifically, results from subgroup analyses of clinical trial data suggest the benefits of denosumab on fracture risk reduction are similar across different age groups in women; this supports removal of the clinical criterion in the 2011 recommendation that age should be greater than 75 years in postmenopausal women with osteoporosis. The Health Canada product monographs for denosumab and bisphosphonates provided evidence to support aligning the 2011 and 2015 recommendations by adding renal impairment as a possible contraindication, as well as unsatisfactory response to bisphosphonates, as additional criteria for reimbursement to the 2011 recommendation for women. The Osteoporosis Canada 2010 guidelines as well as experience from specialist clinical practice suggest that the use of the CAROC or FRAX tools is the most appropriate means by which fracture risk should be assessed, and that the use of these tools can correctly identify patients who will benefit from treatment with denosumab. This supports aligning the two recommendations by referring to these tools for defining fracture risk in the 2011 recommendation for women. Finally, complete alignment of the 2011 recommendation for women requires comparing denosumab with zoledronic acid, as this drug was considered the most appropriate comparator in the CDR review of the osteoporosis in men in 2015. Although there is lower quality evidence suggesting that denosumab may be more effective than zoledronic acid, the results of an RCT and four IDCs are consistent with the conclusion that there are no clinically relevant differences between denosumab and zoledronic acid with respect to fracture risk reduction in postmenopausal women with osteoporosis at risk for fracture. This suggests that the condition of a reduced price for denosumab is applicable to the 2011 recommendation for osteoporosis in women, which will achieve alignment with the 2015 recommendation for men.

APPENDIX 1: METHODOLOGY

Literature Search Methods

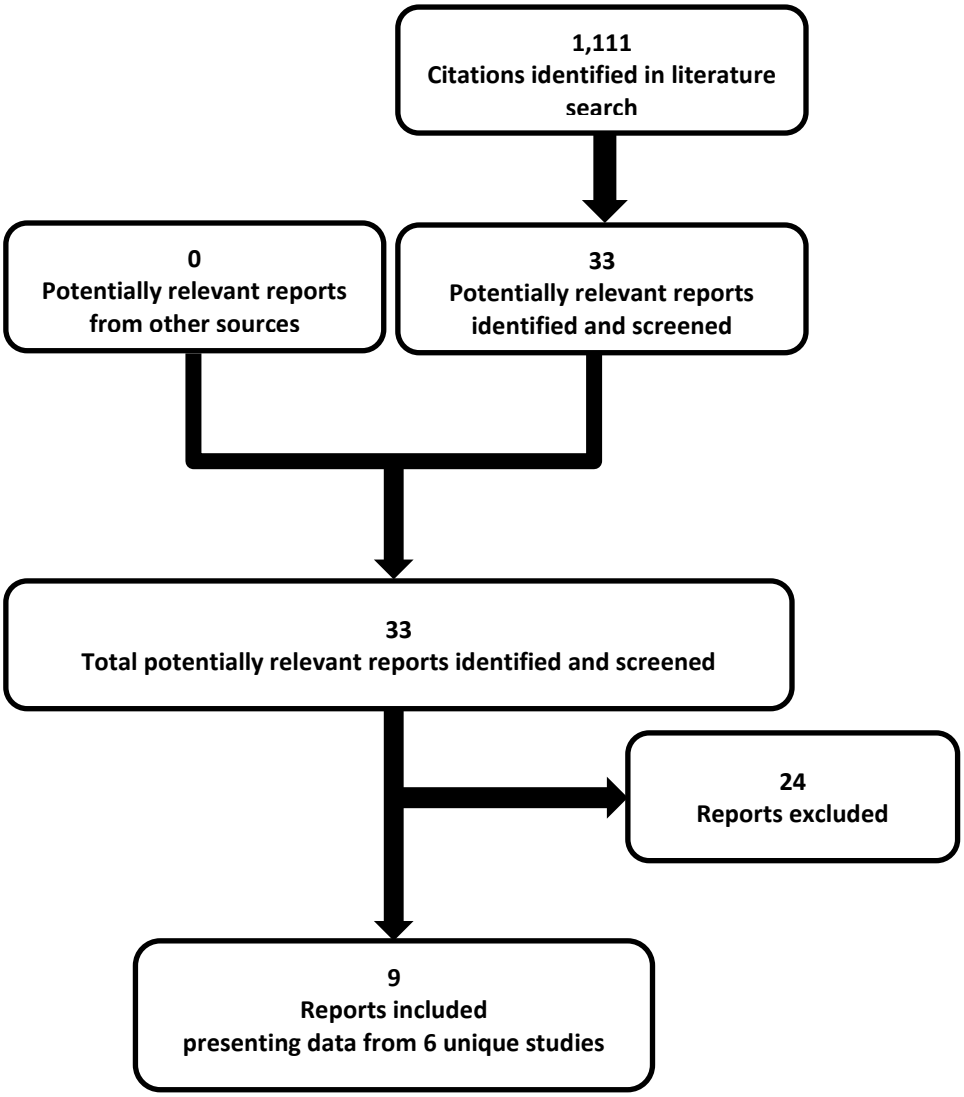
The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates through Ovid; Embase (1974-) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Prolia (denosumab). Methodological filters were applied to limit retrieval to RCTs. Where possible, retrieval was limited to the human population. The search was limited to documents published between January 1, 2010 and December 9, 2015. Retrieval was not limited by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies. The initial search was completed on December 9, 2015. Regular alerts were established to update the search until the CDEC meeting on April 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Analysis Methods

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of reporting of meta-analyses.

APPENDIX 2: 2011 CEDAC RECOMMENDATION FOR POSTMENOPAUSAL WOMEN

CEDAC FINAL RECOMMENDATION

DENOSUMAB
(Prolia — Amgen Canada Inc.)
Indication: Postmenopausal Osteoporosis

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends 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), and have at least two of the following:

- age >75 years
- a prior fragility fracture
- a bone mineral density (BMD) T-score ≤ -2.5.

Reason for the Recommendation:
In one double-blind randomized controlled trial comparing denosumab with placebo in postmenopausal women with low BMD T-scores, denosumab achieved a statistically significantly greater reduction in the incidence of new vertebral and hip fractures, in both the total patient population and a predefined high-risk subgroup. A cost-utility analysis based on the high-risk subgroup resulted in a cost per quality-adjusted life-year (QALY) of $29,000 for denosumab compared with no treatment. The cost per QALY was higher when the total patient population was considered.

Of Note:
The Committee considered the clinical basis for the manufacturer's economic evaluation of denosumab compared with raloxifene, but had concerns regarding the comparability of the patient populations in the clinical trials that were used to inform the economic evaluation.

Background:
Denosumab is indicated by Health Canada for the treatment of postmenopausal women at high risk for osteoporotic (fragility) 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. Denosumab is a fully human monoclonal antibody that inhibits osteoclast-mediated bone resorption. Health Canada recommends that denosumab be administered as a single subcutaneous (SC) injection of 60 mg once every six months. Denosumab 60 mg/mL solution for injection is available as a 1.0 mL single use vial and a 1.0 mL prefilled syringe.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of denosumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included six manufacturer-sponsored RCTs of postmenopausal women with osteoporosis. This diagnosis was based on low BMD as measured by T-scores.

- FREEDOM (N =7,808) was a 36-month double-blind double-dummy parallel-group RCT comparing denosumab 60 mg SC every six months with placebo. FREEDOM predefined a high-risk subgroup (which accounted for 45% of the total patient population); patients in the high-risk subgroup were those who met two of the following: age greater than 70 years; BMD T-score of ≤ -3.0 at the lumbar spine, total hip, or femoral neck; or a prevalent vertebral fracture.
- DECIDE (N = 1,189) and STAND (N = 504) were 12-month double-blind double-dummy parallel-group RCTs comparing denosumab 60 mg SC every six months with alendronate 70 mg orally once weekly. Both the DECIDE and STAND trials were designed to test the non-inferiority of denosumab to alendronate, with pre-planned testing for superiority if denosumab was found to be non-inferior.
- DAPS (N = 250) was a 24-month, open-label, cross-over RCT. Sequences were one year in duration and doses were: denosumab 60 mg SC every six months and alendronate 70 mg orally once weekly.
- Study 20010223 (N=406) was a 48-month parallel-group RCT of mixed double-blind (denosumab and placebo) and open-label (alendronate) designs. The trial consisted of nine treatment groups; seven groups employed different doses of denosumab and one group each used alendronate and placebo. Only the denosumab group employing the Health Canada recommended dose (60 mg SC every six months), for four years, was included in the systematic review. Comparator groups consisted of alendronate (70 mg orally once weekly for two years with two years off of treatment) and placebo (SC injections every three months for two years, followed by every six months for two years).
- Study 20050179 (N=247) was a 12-month double-blind, double-dummy, parallel-group RCT that included three treatment groups: denosumab 60 mg SC every six months, alendronate 70 mg orally once weekly, and placebo.

The frequency of withdrawal was approximately 17% in the FREEDOM trial and did not differ substantially between treatment groups. Of the 7,808 patients enrolled in FREEDOM, 7,393 (95%) underwent spinal radiography at baseline and during at least one follow-up visit. In the DECIDE and STAND trials the frequency of withdrawal among treatment groups ranged from 4% to 6% and did not differ substantially between treatment groups within the trials. In the DAPS trial 8% of patients randomized to denosumab withdrew compared with 14% for alendronate. In study 20010223 17% of patients randomized to denosumab withdrew compared with 37% for placebo. Withdrawals from study 20050179 were not reported.

Outcomes

The primary outcomes in the trials were:

- FREEDOM – incidence of new vertebral fracture on radiograph over 36 months
- DECIDE and STAND – percentage change in total hip BMD from baseline to 12 months
- DAPS – proportion of patients who were adherent to treatment at 12 months
- Study 20010223 – percentage change in lumbar spine BMD from baseline to 12 months
- Study 20050179 – percentage change in cortical thickness at distal radius from baseline to 12 months

Other outcomes were also defined a priori in the CDR systematic review. Of these outcomes the Committee discussed the following: hip fracture, mortality, quality of life, and adverse events. Outcomes of importance mentioned in the four patient group submissions included: reduction in pain, reduction in fracture risk, and function (ability to perform everyday tasks such as lifting objects, working, and household duties). Pain was not a pre-specified outcome in any of the reviewed studies, but was

assessed as part of several quality of life and functional scales (e.g., Osteoporosis Assessment Questionnaire Short Version [OPAQ-SV], European Quality of Life – 5 Dimensions [EQ-5D]), and the Disability/Back Pain Questionnaire. Fracture reduction was the primary outcome in only one trial (FREEDOM); the remaining trials recorded fractures only as patient-reported adverse events which were not necessarily confirmed by radiographs.

Results

Efficacy or Effectiveness

- In the FREEDOM trial, among patients having had both a baseline and at least one follow-up spinal radiograph, the 36-month incidence of radiographically confirmed new vertebral fracture was statistically significantly lower for denosumab (2.3%) compared with placebo (7.2%), based on the absolute risk reduction (ARR): 4.8, 95% confidence interval (CI), 3.9 to 5.8. Further, the 36-month incidence of radiographically confirmed new vertebral fracture among the predefined high-risk subgroup was statistically significantly lower for denosumab (3.5%) compared with placebo (10.0%) based on the ARR: 6.5, 95% CI, 4.8 to 8.2. Similarly, the incidence of new clinical fractures was statistically significantly less for denosumab compared with placebo for both the total and high-risk patient populations.
- In the FREEDOM trial, the 36-month incidence of hip fracture (a secondary outcome) among the total patient population was not statistically significantly different between denosumab (0.7%) and placebo (1.1%) based on the ARR: 0.3, 95% CI, –0.1 to 0.7, but was statistically significant based on the hazard ratio (HR): 0.60, 95% CI, 0.37 to 0.97. The incidence of hip fracture in the predefined high-risk subgroup was statistically significantly lower for denosumab (1.0%) compared with placebo (1.9%), based on the HR: 0.52, 95% CI, 0.29 to 0.91.
- None of the active comparator trials were powered to examine fracture. For the two active comparator trials (DECIDE and STAND) that reported on fracture, as patient-reported adverse events, the frequency of fracture was similar between denosumab and alendronate.
- Non-inferiority of denosumab compared with alendronate was demonstrated in both the DECIDE and STAND trials, based on the per cent change in the total hip BMD T-score at 12 months. Subsequent superiority testing in both STAND and DECIDE identified small but statistically significantly greater increases in BMD T-scores for denosumab compared with alendronate at the lumbar spine, total hip, and femoral neck sites.
- In the FREEDOM trial, there were no statistically significant differences in quality of life or functional ability between denosumab and placebo based on results of the OPAQ-SV and EQ-5D. Further, there were no statistically significant between-treatment differences in scores obtained from the Disability/Back Pain Questionnaire in the FREEDOM trial.
- Pooled data from the DECIDE and STAND trials demonstrated that patient-reported satisfaction with treatment was statistically significantly greater for denosumab compared with alendronate. In the DAPS trial adherence at 12 months was statistically significantly greater for denosumab (87.3%) compared with placebo (76.6%), however the external validity of these data were questionable due to the administration of denosumab at study visits.

Harms (Safety and Tolerability)

- Mortality, serious adverse events, adverse events, and withdrawal due to adverse events were similar between denosumab and placebo in the FREEDOM trial, and between denosumab and alendronate in the STAND and DECIDE trials.
- Two patients in the open-label extension of the FREEDOM trial, developed osteonecrosis of the jaw after being switched from placebo to denosumab.

- The frequency of gastrointestinal events for denosumab treated patients was similar to that observed for placebo and alendronate; however patients with active gastrointestinal disease were excluded.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis in patients with postmenopausal osteoporosis, with characteristics of patients enrolled in the FREEDOM trial, comparing denosumab with alendronate, risedronate and no treatment over a patient lifetime horizon (~ 25 years). A Markov model was created based on the following health states: well (no current fracture); hip fracture; vertebral fracture; wrist fracture; other fracture; post vertebral fracture; post hip fracture; and dead. The relative efficacy of fracture reduction was obtained from the placebo-controlled FREEDOM trial for denosumab, and a meta-analysis conducted by the National Institute for Health and Clinical Excellence (NICE) in the UK for alendronate and risedronate compared to placebo. While the point estimates of fracture reduction are numerically lower for denosumab, these are indirect comparisons as no head-to-head studies with active treatments using fractures as primary outcome were provided. The manufacturer assumed a five year treatment period, and a two year offset time in which the risks of fracture return to the baseline levels linearly over two years after active treatment is stopped (to account for continued benefit of the drug on fracture risk for a period of time after the patient has stopped taking the drug). Estimates of the decrease in quality of life associated with the various fractures were incorporated from the literature, rather than the denosumab trials.

The manufacturer suggested that the cost per QALY of denosumab may be around $61,000 varying up as high as ~$110,000 per QALY in sensitivity analysis, when compared to alendronate; and, for patients unable to take oral bisphosphonates, the cost per QALY for denosumab was $42,915 compared to no treatment, varying as high as $88,935 per QALY. The cost per QALY estimate was less when the manufacturer considered the high-risk subgroup from the FREEDOM trial, which was reported as $29,000 per QALY, when comparing denosumab with no treatment.

The annual cost of denosumab ($660) is greater than oral bisphosphonates ($131 to $332) and raloxifene ($335).

Patient Input Information:

The following is a summary of information provided by four patient groups that responded to the CDR call for patient input.

- Persons with osteoporosis reported reduced mobility and ability to complete day-to-day tasks; for persons with osteoporosis, pain, and the curtailing of activities because of the fear of fractures were felt to have an important impact on patients' quality of life.
- Adherence to taking bisphosphonates can be problematic because of forgetfulness related to daily or weekly dosing.
- Bisphosphonates were considered inconvenient to take (related to taking the drug upon waking on an empty stomach and having to remain upright) and were considered to have important adverse effects (mainly gastrointestinal). Patients feel there is a need for an alternative treatment for those who cannot tolerate bisphosphonates or have not responded to them.

Other Discussion Points:

- The Committee noted that while there are observational studies reporting gastrointestinal adverse events with bisphosphonates, systematic reviews of bisphosphonate trials have not reported important differences in gastrointestinal events compared with placebo.

- It was noted that the statistically significant increase in BMD for denosumab compared with alendronate reported in the STAND trial was for a highly relevant patient population; all patients in the STAND trial had previously taken alendronate for a minimum of six months (median 36 months) and more than 50% had a previous fracture. However, there are no RCTs specifically designed to determine if patients who have experienced a fragility fracture while on a bisphosphonate have a lower incidence of fragility fracture if switched to denosumab compared with the continuation of the bisphosphonate.
- It was unclear if mortality data were captured for all patients enrolled in the FREEDOM trial.
- It was noted that the severity of fractures observed in the trials, both morphological and clinical, was unknown.

APPENDIX 3: 2015 CDEC RECOMMENDATION FOR MEN

CDEC FINAL RECOMMENDATION

DENOSUMAB
(Prolia — Amgen Canada)
Indication: Osteoporosis in Men

Recommendation:
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 (≥ 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 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 postmenopausal 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 with 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 delayed release [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 postmenopausal 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 enrolment 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.

APPENDIX 4: PATIENT INPUT

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed.

CADTH received two patient input submissions from the following patient groups:

- Osteoporosis Canada
- Arthritis Consumer Experts

Each group independently prepared and submitted their input. Information presented in this patient input summary was gathered from several sources:

- All feedback provided by Osteoporosis Canada is based on the evidence that was used to create the 2010 clinical practice guidelines.
- The feedback provided by Arthritis Consumer Experts summarizes the input gathered in the context of postmenopausal osteoporosis from three different persons: one patient living with rheumatoid arthritis and osteoarthritis; one Professor in the Department of Medicine at McMaster University; and one rheumatologist.

1. How should fracture risk be best described?

Osteoporosis Canada recommends in its input submission to use a fracture assessment tool such as CAROC or FRAX that combines clinical risk factors and the result of BMD measured at the hip. The professor and rheumatologist consulted by Arthritis Consumer Experts also recommended using risk assessment tools, while the report from the patient indicated that this person would like to see fracture risk described in terms of individual risk assessed with an appropriate level of detail.

2. Is there a place for age (> 75 years) or bone density scores, or are these adequately captured within fracture risk?

Osteoporosis Canada noted that the use of the fracture assessment tools reliably captures patients who are at high risk of fragility fractures and that age and BMD alone might not reflect accurately the risk of fractures. For example, a patient who has sustained a fragility humerus fracture may have a BMD that is neither below –2.5 nor older than 75 years, yet their risk for future fracture may be higher than 20% and would therefore benefit from an antiresorptive therapy such as denosumab.

The feedback gathered by Arthritis Consumer Experts suggests that age and bone density scores are two strong clinical risk factors for fracture; however, there are several other significant risk factors that must also be considered when assessing fracture risk. Therefore, they felt that fracture risk assessment should not rely only on age or bone density score.

3. How should bisphosphonate failure be best described?

Osteoporosis Canada considers that there is no definite definition of treatment failure. According to the patient group, most would agree that patients who continue to fracture while on therapy for a period of 12 months could be considered as having failed therapy. Other failures of therapy include significant BMD loss despite therapy or persistently elevated bone turnover markers while receiving antiresorptive therapy. The individuals consulted by Arthritis Consumer Experts suggested definitions of bisphosphonate failure that are in line with the aforementioned definition provided by Osteoporosis Canada. These definitions are based on the occurrence of new fracture while on bisphosphonate treatment and/or significant decline in BMD.

4. How should bisphosphonate intolerance be best described?

Osteoporosis Canada suggests the use of the most common side effects of oral bisphosphonates, which are heartburn and irritation of the esophagus. Nausea, abdominal pain, and loose bowel movements may also occur. Bone, joint, and/or muscle pain has been reported infrequently by patients taking bisphosphonates. According to this patient group, there is bisphosphonate intolerance if patients take the medication correctly, adhering to the instructions on how to take a bisphosphonate, and still experience one or more of these side effects to the extent that they cannot tolerate the medication. Osteoporosis Canada also indicates that bisphosphonates should not be administered to patients who have impaired kidney function, and that denosumab should be considered as the optimal choice for treatment in this population.

The feedback gathered by Arthritis Consumer Experts also suggests taking into consideration gastrointestinal adverse events, which are common with bisphosphonates. In this case, the Arthritis Consumer Experts' input suggests adding the following reimbursement criterion to the present CDEC recommendation:

> "Persistent or recurrent gastrointestinal intolerance, despite interventions to control this which will not compromise the absorption of the agent, after at least one month."

While the listed contraindications of hypersensitivity and esophageal abnormalities of stricture or achalasia are reasonable, this fails to take into consideration the patient who simply is intolerant of these drugs (i.e., dyspepsia). Many persons with dyspepsia sufficient to prevent the use of bisphosphonates would not demonstrate either stricture or achalasia at endoscopic and/or radiologic evaluation of the esophagus. According to the CDEC recommendation, these patients would be denied funding for denosumab, although being at high risk for fracture.

APPENDIX 5: COST TABLE

The table below presents the average costs calculated by CADTH for all osteoporosis treatments that have been deemed to be appropriate comparators for denosumab by clinical experts. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table, and as such may not represent the actual costs to public drug plans.

Drug / Comparator	Strength	Dosage Form	Price ($)	Average Use	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Denosumab (Prolia)	60 mg	Prefilled syringe	357.9000	60 mg every 6 months	1.96	716
Zoledronic acid (Aclasta, generics)	5 mg/ 100 mL	Infusion	335.4000 690.9200	Once yearly	0.92 1.89	335 691
Alendronate (generics)	70 mg 10 mg	Tablet	2.5144 0.4987	70 mg weekly or 10 mg daily	0.36 0.50	131 182
Alendronate/ Cholecalciferol (Fosavance, generics)	70 mg/ 70 mcg 70 mg/ 140 mcg	Tablet	3.4969 2.3312	One tablet weekly	0.50 0.33	182 122
Etidronate disodium (generic)[a]	200 mg	Tablet	0.3569	2 tablets daily	0.71	261
Etidronate and calcium carbonate (generic)[a]	400 mg and 500 mg	90-tablet kit	0.2221	1 tablet of etidronate for 14 days, then 1 tablet of calcium for 76 days	0.22	81
Risedronate sodium (generics)	35 mg	Tablet	2.4893	35 mg weekly	0.35	130
Risedronate sodium (Actonel)	35 mg	DR tablet	11.5368	35 mg weekly	1.64	600
To increase bone mass in men with primary or hypogonadal severe osteoporosis						
Teriparatide (Forteo)[b]	250 mcg/mL	2.4 mL or 3 mL pen for s.c. injection	809.73[c]	20 mcg daily	28.92[d]	10,555
DR = delayed release; IU = international units; mcg = micrograms; s.c. = subcutaneous.						

Source: Ontario Drug Benefit (effective January 2016) prices unless otherwise stated.

[a] Not approved for treatment of primary osteoporosis in men.

[b] Teriparatide is indicated for the treatment of postmenopausal women with severe osteoporosis who are at high risk of fracture or who have failed or are intolerant to previous osteoporosis therapy; to increase bone mass in men with primary or hypogonadal severe osteoporosis who have failed or are intolerant to previous osteoporosis therapy; and for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in men and women who are at increased risk for fracture. (Forteo product monograph).

[c] Quebec Formulary, reimbursed for postmenopausal osteoporosis (January 2016).

[d] Daily cost based on product monograph recommendation to dispose of units after 28 days.

Note:

- Vitamin D3 is not reimbursed by a number of participating drug plans. Annual cost of vitamin D3 is $11 [Dose: 400 IU to 800 IU daily as a 400 IU tablet of vitamin D3 priced at $0.0300 (Quebec Drug Benefit Formulary-RAMQ, January 2016).
- Annual cost of calcium carbonate is $24 [Dose: 1,500 mg daily given as 500 mg tablet of calcium carbonate 3 times daily (generic) priced at $0.0216 (Quebec Drug Benefit Formulary-RAMQ, January 2016).

REFERENCES

1. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009 Aug 20;361(8):756-65.
2. Palacios S, Kalouche-Khalil L, Rizzoli R, Zapalowski C, Resch H, Adachi JD, et al. Treatment with denosumab reduces secondary fracture risk in women with postmenopausal osteoporosis. Climacteric. 2015 Dec;18(6):805-12.
3. McClung MR, Boonen S, Torring O, Roux C, Rizzoli R, Bone HG, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. J Bone Miner Res [Internet]. 2012 Jan [cited 2015 Dec 15];27(1):211-8. Available from: http://onlinelibrary.wiley.com/doi/10.1002/jbmr.536/epdf
4. Boonen S, Adachi JD, Man Z, Cummings SR, Lippuner K, Torring O, et al. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. J Clin Endocrinol Metab [Internet]. 2011 Jun [cited 2015 Dec 15];96(6):1727-36. Available from: http://press.endocrine.org/doi/pdf/10.1210/jc.2010-2784
5. McCloskey EV, Johansson H, Oden A, Austin M, Siris E, Wang A, et al. Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. J Bone Miner Res [Internet]. 2012 Jul [cited 2015 Dec 15];27(7):1480-6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/jbmr.1606/epdf
6. Prolia (denosumab): 60 mg/mL solution for injection [product monograph]. Mississauga (ON): Amgen Canada Inc.; 2014 Oct 20.
7. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ [Internet]. 2010 Nov 23 [cited 2016 Jan 11];182(17):1864-73. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988535
8. Anastasilakis AD, Polyzos SA, Gkiomisi A, Saridakis ZG, Digkas D, Bisbinas I, et al. Denosumab versus zoledronic acid in patients previously treated with zoledronic acid. Osteoporos Int. 2015;26(10):2521-7.
9. Miller PD, Pannacciulli N, Brown JP, Czerwinski E, Nedergaard BS, Bolognese MA, et al. A randomized double-blind study of denosumab compared with zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonate [Internet]. Abstract presented at: 2015 ACR/ARHP Annual Meeting; 2015 Nov 8; San Francisco. [cited 2016 Mar 23]. Available from: http://acrabstracts.org/abstract/a-randomized-double-blind-study-of-denosumab-compared-with-zoledronic-acid-in-postmenopausal-women-with-osteoporosis-previously-treated-with-oral-bisphosphonate/
10. Migliore A, Broccoli S, Massafra U, Cassol M, Frediani B. Ranking antireabsorptive agents to prevent vertebral fractures in postmenopausal osteoporosis by mixed treatment comparison meta-analysis. Eur Rev Med Pharmacol Sci [Internet]. 2013 Mar [cited 2015 Dec 15];17(5):658-67. Available from: http://www.europeanreview.org/wp/wp-content/uploads/658-667.pdf
11. Freemantle N, Cooper C, Diez-Perez A, Gitlin M, Radcliffe H, Shepherd S, et al. Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. Osteoporos Int [Internet]. 2013 Jan [cited 2015 Dec 15];24(1):209-17. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3662000/pdf/emss-53243.pdf

12. Murad MH, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA, et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. J Clin Endocrinol Metab [Internet]. 2012 Jun [cited 2015 Dec 15];97(6):1871-80. Available from: http://press.endocrine.org/doi/pdf/10.1210/jc.2011-3060

13. Hopkins RB, Goeree R, Pullenayegum E, Adachi JD, Papaioannou A, Xie F, et al. The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. BMC Musculoskelet Disord [Internet]. 2011 [cited 2015 Dec 15];12:209. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196921/pdf/1471-2474-12-209.pdf