Common Drug Review
Pharmacoeconomic Review Report

October 2015

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
Listing request	As per indication
Dosage form(s)	60 mg/mL solution for injection
NOC date	November 21, 2012
Manufacturer	Amgen Canada

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 CADTH 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient group submissions.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 CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

BMD	bone mineral density
CDR	CADTH Common Drug Review
HTA	health technology assessment
IDC	indirect comparison
PBAC	Pharmaceutical Benefits Advisory Committee

SUMMARY

Background

Denosumab is available as a 60 mg/mL pre-filled syringe at a cost of $357.90 (Ontario Drug Benefit, June 2015).[1] At the recommended dose of 60 mg every six months, the annual cost of denosumab is $716.

Denosumab was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) in 2011 and was recommended for treatment of osteoporosis in post-menopausal women.[2]

Approach for This Review

As this review was initiated by the participating drug plans, the manufacturer of denosumab was invited to submit clinical and/or economic information but was not obligated to do so. The manufacturer provided an indirect comparison (IDC) of denosumab and other comparators to support the clinical review but did not include an economic evaluation for denosumab. As such, the CADTH Common Drug Review (CDR) is limited to cost and economic information available in the public domain.

Review of Published Literature

Given the information available, CDR conducted a review of the literature to determine whether there were any published economic evaluations that could help address the cost-effectiveness of denosumab compared with other pharmacologic 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, that would be applicable to the Canadian setting.

Few economic evaluations have been published addressing the research questions for this review. Only one study was identified: an industry-sponsored study by Parthan et al. that assessed denosumab versus other treatments in Swedish men with osteoporosis who are ≥ 75 years of age using a cost-utility analysis with a lifetime time horizon.[3] In the analysis, denosumab was compared with generic alendronate, generic risedronate, ibandronate, zoledronate, strontium ranelate, and teriparatide. Results of the study by Parthan et al. showed denosumab had the lowest cost and highest quality-adjusted life-years, therefore dominating all comparators, including generic bisphosphonates, in treatment of osteoporosis in men ≥ 75 years old in Sweden.[3] However, given the uncertainty over the assumptions of similarity of clinical efficacy of denosumab in both men and women, the generalizability of osteoporosis in male populations between Sweden and Canada, and concern over the industry sponsorship for the study, its applicability to inform this review was limited.

A health technology assessment (HTA) review from Australia's Pharmaceutical Benefits Advisory Committee (PBAC) was identified as part of the literature search. The PBAC review of denosumab recommended its use as an antiresorptive drug for treatment and prevention of osteoporosis in men over the age of 70 years and with a bone mineral density (BMD) T-score of –2.5 or less. Further detail on the PBAC review of denosumab is provided in Appendix 2 of this report.

Cost Comparison

As a result, a cost comparison was conducted by CDR from the public health care payer's perspective to compare the cost of denosumab with zoledronic acid, as both treatments are available in injectable dosage forms — denosumab as a subcutaneous injection and zoledronic acid as intravenous infusion. 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 in men and was deemed by the clinical expert to be a treatment reserved for severe osteoporosis, and would be only considered as a third-line treatment option after oral and subsequently intravenous bisphosphonates.

Clinical evidence to support comparing the costs of denosumab to zoledronic acid was based on the IDC provided by the manufacturer[4] comparing efficacy outcomes and adverse events based on four trials.[5-8] The IDC provided two sets of comparisons between denosumab and zoledronic acid (one- and two-step indirect comparisons). The two-step indirect comparison used the placebo reference groups from the ADAMO[5] and Orwoll[7] studies and the alendronate reference groups from the Orwoll[7] and Study 2308[8] studies. Relative to zoledronic acid, denosumab was associated with a statistically significant increase in BMD of the lumbar spine, but no statistically significant differences for BMD at the other skeletal sites (e.g., femoral neck, hip/total hip, and trochanter). The one-step indirect comparison of denosumab and zoledronic acid used placebo as the common reference, which was based on ADAMO[5] and Boonen.[6] In conclusion, the results of the two IDCs provided by the manufacturer comparing denosumab with zoledronic acid 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. The available evidence also suggested that denosumab and zoledronic acid do not have markedly different safety profiles despite that harms were not analyzed in the IDC.

The IDC did not provide a comparison of denosumab to oral bisphosphonates (alendronate or risedronate) that are considered potentially relevant comparators based on feedback from the clinical expert. Additionally, the IDC did not conduct a systematic literature review for the included alendronate studies. Further detail for the IDC is provided in Appendix 7 of the CDR Clinical Review Report for denosumab.

Results/Conclusions

At current publicly available prices and recommended doses, the annual cost of denosumab (60 mg every six months; $716) is more expensive than generic zoledronic acid (5 mg/100 mL once yearly; $335) and comparable to zoledronic acid (Aclasta; 5 mg/100 mL once yearly; $691), Table 1. Denosumab is more expensive compared with oral bisphosphonates, with incremental annual cost between $116 and $594 for generic alendronate (70 mg weekly or 10 mg daily; $131 to $181), generic alendronate/cholecalciferol (70 mg/70 mcg or 70 mg/140 mcg weekly; $122 to $182), risedronate (Actonel DR; 35 mg weekly; $600), and generic risedronate (35 mg weekly; $130).

Using price reduction reanalyses, for denosumab to reach cost neutrality with zoledronic acid and oral bisphosphonates, the unit price for denosumab would require reduction between 4% to 84% (refer to Appendix 1 in this report for more detail).

Cost Comparison Table

The comparators presented in Table 1 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 1: DRUGS FOR MALE OSTEOPOROSIS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Average Use	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Denosumab (Prolia)	60 mg	Pre-filled syringe	357.9000	60 mg every 6 months	1.96	716
Treatment of primary osteoporosis in men						
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
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)[a]	250 mcg/mL	2.4 mL or 3 mL pen for SC injection	809.73[b]	20 mcg daily	28.92[c]	10,555

DR = delayed release; SC = subcutaneous.

[a] Teriparatide as indicated for the treatment of post-menopausal women with severe osteoporosis who are at high risk of fracture or who have failed or 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).[9]

[b] Quebec Formulary, reimbursed for post-menopausal osteoporosis (June 2015).[10]

[c] Daily cost based on monograph recommendation to dispose of units after 28 days.[9]

Source: Ontario Drug Benefit (effective June 2015) prices unless otherwise stated.[1]

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 400 IU tablet of vitamin D3 priced at $0.0300 [Quebec Drug Benefit Formulary-RAMQ, June 2015]).[10]
- Annual cost of calcium carbonate is $24 (dose: 1,500 mg daily given as 500 mg tablet of calcium carbonate three times daily [generic] priced at $0.0216 [Quebec Drug Benefit Formulary-RAMQ, June 2015]).[10]

APPENDIX 1: PRICE REDUCTION ANALYSIS

For denosumab to reach cost neutrality with zoledronic acid and oral bisphosphonates, the unit price for denosumab would require reduction between 4% (zoledronic acid, Aclasta) to 84% (generic alendronate/cholecalciferol) (Table 2).

TABLE 2: PRICE REDUCTION ANALYSIS FOR DENOSUMAB

	Price ($/unit)	Annual Cost ($)	Incremental Annual Cost vs. Denosumab ($)	% Reduction for Denosumab to Achieve Cost Neutrality
Denosumab 60 mg	357.9000	716	-	-
Zoledronic acid 5 mg/ 100 mL (Aclasta)	690.9200	691	25	4
Zoledronic acid 5 mg/ 100 mL (generic)	335.4000	335	381	54
Alendronate (10 mg)	0.4987	182	534	75
Alendronate (70 mg)	2.5144	131	585	82
Alendronate/cholecalciferol (70 mg/140 mcg)	2.3312	122	594	84
Alendronate/cholecalciferol (70 mg/70 mcg)	3.4969	182	534	75
Risedronate 35 mg	2.4893	130	586	82
Risedronate 35 mg (delayed release)	11.5368	600	116	16

vs. = versus.

APPENDIX 2: PUBLISHED HEALTH TECHNOLOGY ASSESSMENT REVIEW

A health technology assessment (HTA) review from Australia's Pharmaceutical Benefits Advisory Committee (PBAC) was also identified as part of the literature search. PBAC reviewed denosumab and recommended its use as an antiresorptive drug for treatment and prevention of osteoporosis in men.[11] The PBAC review was based on a cost-minimization analysis submitted by the manufacturer, supported by an indirect comparison of denosumab to zoledronic acid. All details of the economic information were not publicly made available (Table 3). The PBAC recommendation specified that patients eligible for denosumab must be aged 70 years or older and must have a bone mineral density (BMD) T-score of –2.5 or less. The PBAC review appears to be based on a similar IDC to that provided to CADTH Common Drug Review (CDR), with similar information on the included trials and comparators, and eligible patient population for this indication. This supports CDR's approach to considering a cost comparison of denosumab to zoledronic acid and other treatments that are approved for this indication in Canada. No other HTA reviews for denosumab use in men were available.

TABLE 3: SUMMARY TABLE OF HEALTH TECHNOLOGY ASSESSMENT FOR DENOSUMAB

	PBAC[11]
Date of publication	July 2013[a]
Drug	60 mg/mL injection, 1 mL pre-filled syringe x 1
Price	Not stated
Treatment	60 mg once every six months
Comparator	Zoledronic acid; 5 mg once every 12 months
Population modelled	Male osteoporosis patients aged 70 years of age or older with a bone mineral density T-score of –2.5 or less
Type of model	Cost-minimization analysis
Time horizon	Not stated
Cycle length	
Discount rate	
Key outcomes	
Results	
Sources of uncertainty — identified by PBAC	• The pricing of treatment with denosumab did not appear to take into account the two doctor visits required for obtaining the denosumab prescriptions compared with one doctor visit for zoledronic acid. • The cost of monitoring calcium levels after receiving denosumab (due to the risk of hypocalcemia) and the additional costs for treating denosumab adverse events were not included.
Recommendation	PBAC recommended the listing of denosumab as an antiresorptive drug for treatment and prevention of osteoporosis in men.
CDR assessment	The cost-minimization analysis initiated by CDR appears to be similar to the cost-minimization analysis submitted to PBAC, although specific details of the analysis were not publicly made available.

CDR = CADTH Common Drug Review; PBAC = Australia's Pharmaceutical Benefits Advisory Committee.
[a] Publication date not stated; date of meeting used instead.

REFERENCES

1. Ontario Ministry of Health and Long-Term Care [Internet]. Toronto: MOHLTC; 2015 Apr 24. Drugs funded by Ontario Drug Benefit (ODB) program: e-formulary; 2015 [cited 2015 Apr 27]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf_eformulary.aspx
2. Common Drug Review. CEDAC final recommendation: denosumab (Prolia – Amgen Canada Inc.) indication: postmenopausal osteoporosis [Internet]. Ottawa: CADTH; 2015 Mar 30. [cited 2015 Jun 10]. Available from: https://www.cadth.ca/media/cdr/complete/cdr_complete_Prolia_April-1-11.pdf
3. Parthan A, Kruse M, Agodoa I, Silverman S, Orwoll E. Denosumab: a cost-effective alternative for older men with osteoporosis from a Swedish payer perspective. Bone. 2014;59:105-13.
4. Indirect comparison: denosumab vs zoledronic acid [**CONFIDENTIAL** internal manufacturer's report]. North Ryde NSW (Australia): Amgen Australia PTY Ltd; 2013 Mar.
5. Orwoll E, Teglbjaerg CS, Langdahl BL, Chapurlat R, Czerwinski E, Kendler DL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab [Internet]. 2012 Sep [cited 2015 Apr 20];97(9):3161-9. Available from: http://press.endocrine.org/doi/pdf/10.1210/jc.2012-1569
6. Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J, Langdahl B, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med. 2012 Nov;367(18):1714-23.
7. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med [Internet]. 2000 Aug 31 [cited 2015 Apr 20];343(9):604-10. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJM200008313430902
8. Orwoll ES, Miller PD, Adachi JD, Brown J, Adler RA, Kendler D, et al. Efficacy and safety of a once-yearly i.v. Infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study. J Bone Miner Res [Internet]. 2010 Oct [cited 2015 Apr 20];25(10):2239-50. Available from: http://onlinelibrary.wiley.com/doi/10.1002/jbmr.119/epdf
9. Forteo® (teriparatide (rDNA origin) injection): 250 mcg/mL in 3 mL prefilled pen, 250 mcg/mL in 2.4 mL prefilled pen [product monograph] [Internet]. Toronto: Eli Lilly Canada Inc.; 2010 Feb 9. [cited 2015 Apr 27]. Available from: http://www.lilly.ca/en/pdf/product-monograph/4.0_forteo-pm_9feb10_clean.pdf
10. Regie de l'assurance maladie Quebec [Internet]. Quebec (QC): Gouvernement du Quebec; c2014. Liste des medicaments; 2015 [cited 2015 Apr 27]. Available from: http://www.ramq.gouv.qc.ca/fr/regie/publications-legales/Pages/liste-medicaments.aspx#
11. Pharmaceutical Benefit Advisory Committee. Public summary document. Product: denosumab, injection, 60 mg/mL, Prolia® [Internet]. Canberra: Pharmaceutical Benefits Scheme; 2013 Jul. [cited 2015 Apr 27]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2013-07/denosumab-psd-07-2013.pdf