Common Drug Review
Pharmacoeconomic Review Report

November 2016

Drug	Denosumab (Xgeva)
Indication	Treatment to reduce the risk of developing skeletal-related events in patients with bone metastases from breast cancer, prostate cancer, non–small cell lung cancer, and other solid tumours
Listing request	Treatment to reduce the risk of developing skeletal-related events in patients with bone metastases from solid tumours (other than breast and prostate cancer), including non–small cell lung cancer
Dosage form(s)	120 mg/1.7 mL solution for subcutaneous injection
NOC date	May 10, 2011
Manufacturer	Amgen Canada Inc.

Denosumab (Xgeva) Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health (CADTH) and not those of IMS Health Canada Inc.

This review report was prepared by CADTH. In addition to CADTH staff, the review team included a clinical expert in oncology 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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 the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
BSC	best supportive care
CDR	CADTH Common Drug Review
ICER	incremental cost-effectiveness ratio
NMA	network meta-analysis
NSCLC	non–small cell lung cancer
OST	other solid tumours
PAS	patient access scheme
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SRE	skeletal-related event
WTP	willingness to pay

SUMMARY

Background

Denosumab is being reviewed for the patient population with bone metastases secondary to other solid tumours (OST). A concurrent submission to CDR for patients with bone metastases from breast cancer is currently being reviewed.

Denosumab (Xgeva) is available as a 120 mg/1.7mL single-use vial of solution for injection at a cost of $575.55 per vial (Ontario Drug Benefit Exceptional Access Formulary, October 2015).[1] At the recommended dose of 120 mg/1.7mL every four weeks, the annual cost of denosumab is $7,482.

Denosumab (Xgeva) was reviewed by the Canadian Drug Expert Committee (CDEC) in 2011 and was recommended for prevention of skeletal-related events (SREs) in patients with castrate-resistant prostate cancer with one or more documented bony metastases and good performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of 0 to 2), in jurisdictions listing zoledronic acid for the same indication.[2]

Approach to This Review

This review was initiated by the Formulary Working Group (FWG) for the drug plans participating in the CADTH Common Drug Review (CDR) program. The manufacturer of denosumab was invited to submit clinical and/or economic information but was not obligated to do so. The manufacturer did not provide an economic model for the population of patients with bone metastases from non–small cell lung cancer (NSCLC) and OST; however, it did provide the report submitted to the National Institute for Health and Care Excellence (NICE) in the UK that included a population with NSCLC and OST.

As no economic information was provided to directly address the cost-effectiveness of denosumab for this indication in Canada, CDR relied on the information available to CDR regarding comparative clinical effectiveness — as assessed by the CDR clinical reviewers — to determine the appropriate type of economic evaluation to address the question of cost-effectiveness (e.g., whether a cost-effectiveness analysis or cost-minimization analysis is warranted). In the absence of the provision of Canadian economic information, CDR also undertook a literature review to appraise the economic literature for the population with OST (including NSCLC) to supplement the clinical and economic evidence provided to CDR.

Cost Comparison

An economic evaluation was not provided in support of this review. The CDR clinical review team, in its assessment of the clinical data for patients with bone metastases secondary to OST, found that denosumab is non-inferior to zoledronic acid in reducing the time to a first SRE, based on the head-to-head phase 3 clinical trial from Other Solid Tumours Study 20050244 (Other Solid Tumours Study 244),[3,4] although in a secondary analysis, in which multiple myeloma patients were removed and following adjustment for multiplicity, denosumab was superior to zoledronic acid for the same end point.

The manufacturer supplied CDR with information from an indirect treatment comparison submitted to NICE that includes a comparison of denosumab with zoledronic acid and placebo in the OST population. This same indirect treatment comparison was more comprehensively reported by Ford et al.[5] The CDR clinical reviewers found the results to be consistent with the conclusion that denosumab is at least as effective as zoledronic acid and superior to placebo for reducing the risk of a first SRE in patients with

advanced bone metastases from solid tumours; however, CDR noted substantial uncertainty surrounding the results of the indirect treatment comparison. Further details for the indirect treatment comparison are provided in Appendix 7 of the CDR Clinical Review Report for denosumab. No information (direct head-to-head or otherwise) was provided to CDR to assess the comparison of denosumab versus pamidronate or clodronate for patients with bone metastases secondary to OST.

As a result of the clinical findings, a cost comparison was conducted by CDR from the public health care payer's perspective to compare the cost of denosumab (subcutaneous injection) with the intravenously infused zoledronic acid (Zometa, generics) and pamidronate (Aredia, generics), and oral clodronate (tablet) (Table 1). Other comparators such as oral bisphosphonates (alendronate/cholecalciferol, alendronate, etidronate, and risedronate) were not considered based on clinical expert opinion. The lower-strength form of zoledronic acid (Aclasta) was not considered as it is not approved for use in patients with bone metastases secondary to OST. The prices of clodronate and denosumab were sourced from the Ontario Drug Benefit Formulary[6] and Exceptional Access Program[1] respectively, while the prices for zoledronic acid (Zometa) and pamidronate were sourced from the Alberta Blue Cross Formulary[7] because as of November 2015 neither had prices listed on the Ontario formulary.

Summary of the Published Economic Information

CDR undertook a review of the economic literature of denosumab for patients with bone metastases secondary to OST. The literature search was undertaken by an information specialist and identified 150 economic abstracts, of which nine received full text review (Ford et al.,[5] Yfantopoulos et al.,[8] Stopeck et al.,[9] Lothgren et al.,[10] Carter et al.,[11,12] Xie et al.,[13] Snedecor et al.,[14] and Koo et al.[15]). Reviews that: did not stratify the population by cancer type or by bisphosphonate; undertook analyses of denosumab versus placebo; presented results for the breast cancer or prostate cancer indications, but not the OST or NSCLC indications; or were reviews of studies that were already captured in the literature search were not included in the review of the literature. The included reports are summarized below, with a more complete review provided in Appendix 3: Review of the Published Literature.

Four economic evaluations of denosumab were identified for patients with bone metastases secondary to OST (not including prostate or breast cancers). Three of the four studies were industry-sponsored — two by Amgen (Stopeck et al.[9] and Lothgren et al.[10]) and one by Novartis (Yfantopoulos et al.[8]) — and one was a study by an independent review group (Ford et al.[5]).

In all of the studies, the primary comparator for denosumab was zoledronic acid. The study by Ford et al.[5] presented analyses comparing denosumab with best supportive care (BSC) and other bisphosphonates (including pamidronate disodium). One study (Lothgren et al.[10]) was a European budget impact assessment based on a patient switching from zoledronic acid to denosumab. The study reported cost savings of between €1,861 and €3,408 with the use of denosumab for patients with OST. The other three studies presented cost-effectiveness analyses of denosumab versus the current standard of therapy. Focusing on the primary comparator of the studies (zoledronic acid), the study results varied substantially. The study by Stopeck et al.[9] reported higher incremental quality-adjusted life-years (QALYs; 0.06) compared with the studies by Ford et al.[5] (0.004 to 0.008) and Yfantopoulos et al.[8] (0.0046 to 0.005). The costed resource items appear to have been similar across the studies (SRE, drug acquisition, drug administration); however, the costs varied substantially between studies, based primarily on the setting. The incremental cost-effectiveness ratios (ICERs) ranged from £5,400 per QALY with a patient access scheme[5] (PAS) (exchange rate 2010 £ to 2010 C$: £1 = C$1.5918)[16] to €330,000 per QALY[8] (exchange rate 2012 € to 2012 C$: €1 = C$1.2850).[16] Without the patient access, the ICER was assessed to be greater than £200,000 per QALY[5] (exchange rate 2010 £ to 2010 C$: £1 = C$1.5918).[16]

Common to each of these studies and without a patient access scheme in place, at a willingness to pay of C$50,000 per QALY, denosumab was not cost-effective. A noteworthy observation from the review of published cost-effectiveness analyses for this population is that the findings of the randomized controlled trial (RCT) and network meta-analysis (NMA) indicate small, but non-significant differences between denosumab and zoledronic acid. The results of the published economic evaluation appear to be generally consistent with the CDR analysis: denosumab may be associated with a minimal incremental benefit, while being associated with an incremental treatment cost.

Issues for Consideration

CDR identified the following issues for consideration:

- The appropriate comparator for denosumab differs by jurisdiction based on reimbursed treatments. Different reimbursement policies around the comparators and/or prices will alter the value of the analysis undertaken by CDR.
- Generic forms of pamidronate and zoledronic acid are available in some jurisdictions.
- The funding of infusion costs (related to pamidronate and zoledronic acid in this case) remains uncertain. CDR undertook the base case using the assumption that infusion costs are funded by the manufacturer, while a sensitivity analysis explored the results if the province funded the infusion costs.

Results and Conclusions

Based on the CDR clinical review, the data suggest that denosumab (Xgeva) is at least as effective as zoledronic acid in reducing the time to a first SRE in patients with OST. When considering only drug prices, at the current publicly available prices and recommended doses, the annual cost of denosumab (120 mg every four weeks; $7,482 [Ontario Drug Benefit (OBD) formulary list price]) is more expensive than generic zoledronic acid (4 mg/5mL every three to four weeks; $2,521 to $3,361 annually), and comparable to branded zoledronic acid (Zometa; 4 mg/5mL every three to four weeks; $7,203 to $9,604 annually), based on Alberta Drug Benefit list prices. In a scenario where administration costs were not covered by manufacturers, denosumab (120 mg every four weeks) remained more expensive than generic zoledronic acid (4 mg/5mL every four weeks; $7,513 vs. $5,088 annually).

No clinical comparison of denosumab to pamidronate or clodronate was identified; however, denosumab is more expensive than generic pamidronate (90 mg every three to four weeks; $1,182 to $1,577 [Alberta]), and clodronate (1,600 mg to 2,400 mg daily; $1,764 to $4,288 [ODB]); but comparable to branded pamidronate (90 mg every three to four weeks; $6,510 to $8,680 [Alberta]), Table 1. In a scenario where administration costs were not covered by manufacturers, denosumab (120 mg every four weeks) remained more expensive than generic pamidronate (90 mg every four weeks; $7,513 vs. $4,354 annually), Table 3.

The price of denosumab would need to be reduced to be similar to generic zoledronic acid and generic pamidronate. The extent of the price reduction required will depend on the list prices of comparators (which vary by jurisdiction) and whether manufacturers pay for infusion costs.

Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. 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. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR DENOSUMAB FOR THE TREATMENT OF BONE METASTASES IN PATIENTS WITH OTHER SOLID TUMOURS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Denosumab (Xgeva)	**120 mg**	**Pre-filled syringe**	**575.5500**	**120 mg every 4 weeks**	**7,482**
Pamidronate (Aredia)^	30 mg/10 mL 60 mg/10 mL 90 mg/10 mL	Infusion	16.6930[a] NA 50.0790[a]	90 mg every 3[b] to 4 weeks	6,510 to 8,680
Pamidronate (generic)^	30 mg/10 mL 60 mg/10 mL 90 mg/10 mL	Infusion	3.0317[a] NA 9.0953[a]	90 mg every 3[b] to 4 weeks	1,182 to 1,577
Zoledronic acid (Zometa)	4 mg/5 mL	Infusion	110.8160[a]	4 mg every 3 to 4 weeks	7,203 to 9,604
Zoledronic acid (generics)	4 mg/5 mL	Infusion	38.7856[a]	4 mg every 3 to 4 weeks	2,521 to 3,361
Clodronate (Clasteon)	400 mg	Capsule	1.2083	1,600 mg to 2,400 mg daily (3,200 mg maximum)	1,764 to 2,646 3,528
Clodronate (Bonefos)	400 mg	Capsule	1.9582	1,600 mg to 3,200 mg daily	2,859 to 5,718

NA = not available.

[a] Alberta formulary (August 2015).[7] Prices listed are unit prices. Unit price is per mL. The unit price differs to the funded price based on Alberta's Least Cost Alternative (LCA) and Maximum Allowable Cost (MAC). Alberta's supplementary health plans will pay for the LCA or MAC where interchangeable products can be used to fill a prescription. Beneficiaries who choose higher cost alternatives are responsible for paying the difference in price.

[b] If patient receives chemotherapy every 3 weeks, then receives pamidronate every 3 weeks.[17,18]

Source: Ontario Drug Benefit (effective October 2015)[6] prices unless otherwise stated.

Note: Denosumab (Prolia) is also available in a 60 mg pre-filled syringe for osteoporosis but is not being considered as part of this review.

APPENDIX 1: PRICE REDUCTION ANALYSIS

Using the CDR base case (infusions funded by the manufacturer), for denosumab to reach cost neutrality with the listed comparators, the unit price for denosumab would require a reduction between 4% (zoledronic acid, Zometa) to 84% (generic pamidronate) (Table 2).

TABLE 2: CADTH COMMON DRUG REVIEW PRICE REDUCTION SCENARIO FOR DENOSUMAB

	Price ($/unit)	Annual Cost ($)	Incremental Annual Cost vs. Denosumab ($)	% Reduction for Denosumab to Achieve Cost Neutrality
Denosumab 120 mg	575.5500	7,482	NA	NA
Pamidronate 90 mg/10 mL (Aredia)	50.0790[a]	6,510	– 972	13
Pamidronate 90 mg/10 mL (generic)	9.0953[a]	1,182	–6,300	84
Zoledronic acid 4 mg/5 mL (Zometa)	110.8160[a]	7,203	–279	4
Zoledronic acid 4 mg/5 mL (generics)	38.7856[a]	2,521	–4,961	66
Clodronate 400 mg (Clasteon)	1.2083	1,764	–5,718	76
Clodronate 400 mg (Bonefos)	1.9582	2,859	–4,623	62

NA = not available; vs. = versus.
[a] Alberta formulary (August 2015). Unit price is per mL.[7]
Note: Pamidronate and zoledronic acid were assumed to be dosed every 4 weeks
Source: Ontario Drug Benefit (effective October 2015) prices unless otherwise stated.[1,6]

APPENDIX 2: SCENARIO ANALYSIS (INFUSIONS NOT COVERED BY MANUFACTURER)

The infusion costs associated with the use of zoledronic acid and pamidronate may not be funded by the manufacturer in all jurisdictions. In jurisdictions where the infusion cost is a burden to the public health system, the total cost of treatment includes drug acquisition and drug administration (Table 3). Current drug administration costs were not publicly available, thus the below estimates are based on information supplied by the manufacturer for the breast cancer indication, which may or may not be appropriate.[19]

TABLE 3: CADTH COMMON DRUG REVIEW SCENARIO ANALYSIS: INFUSION FUNDED BY PROVINCE

	Annual Drug Acquisition Cost ($)	Annual Drug Administration Cost[a] ($)	Total Annual Treatment Cost ($)	Incremental Annual Cost vs. Denosumab ($)
Denosumab 120 mg	7,482	31	7,513	-
Pamidronate 90 mg/10 mL (Aredia)[b]	6,510	3,172	9,682	2,169
Pamidronate 90 mg/10 mL (generic)[b]	1,182	3,172	4,354	–3,159
Zoledronic acid 4 mg/5 mL (Zometa)[b]	7,203	2,567	9,770	2,257
Zoledronic acid 4 mg/5 mL (generics)[b]	2,521	2,567	5,088	–2,425
Clodronate 400 mg (Clasteon)	1,764	31	1,795	–5,718
Clodronate 400 mg (Bonefos)	2,859	31	2,890	–4,623

vs. = versus.

[a] Drug administration cost is assumed to include only infusion and supply costs for pamidronate and zoledronic acid.[19] Annual cost based on number of infusions per year (13) multiplied by cost of administration supplies ($6.67) and time ($190.83 for zoledronic acid and $237.30 for pamidronate).[19,20] For denosumab, a visit cost has been included as per the breast cancer model.[19] An assumption was made that this cost would be applicable to clodronate as well.

[b] Price based on data from the Alberta drug formulary (August 2015).[7]

Note: Pamidronate and zoledronic acid were assumed to be dosed every 4 weeks

Source: Ontario Drug Benefit (effective October 2015) prices unless otherwise stated.[1,6]

APPENDIX 3: REVIEW OF THE PUBLISHED LITERATURE

The CADTH Common Drug Review (CDR) undertook a review of the economic literature for patients with bone metastases secondary to other solid tumours (OST). The 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 and daily updates through Ovid; Embase (1974–)through Ovid; PubMed, and the University of York Centre for Reviews and Dissemination NHS Economic Evaluations Database. 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 denosumab (Xgeva) and bone metastases.

Methodological filters were applied to limit retrieval to economic studies. The search was run on August 28, 2015. Retrieval was not limited by publication year or language.

Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on January 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), which includes the websites of health technology assessment (HTA) agencies and other economics-related resources. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

The search identified 150 economic abstracts, of which nine were retrieved for full text review (Ford et al.,[5] Yfantopoulos et al.,[8] Stopeck et al.,[9] Lothgren et al.,[10] Carter et al.,[11,12] Xie et al.,[13] Snedecor et al.,[14] and Koo et al.[15]) based on the following list of inclusion criteria:

- economic evaluation (cost-effectiveness analysis, cost-minimization analysis, budget impact assessment)
- population was bone metastases in patients with solid tumours (excluding prostate cancer)
- comparison of denosumab versus zoledronic acid, pamidronate, or clodronate
- full articles only (articles in abstract form, letters, conference posters were not included given the limited information provided).

These nine articles underwent full text review. Articles that did not stratify the population by cancer type or by bisphosphonate,[11] did not present results for the OST or non–small cell lung cancer (NSCLC) indications,[12-14] or were reviews of studies that were already captured in the literature search[15] were not included in the review of the literature. A further five economic articles[21-25] and two HTA reports were identified distinctly from a review of the grey literature. None of the articles identified in the grey literature search met the criteria for inclusion in the literature review; the HTA reports are reported in Appendix 4: Published Health Technology Assessment Reports.

The literature search identified four economic evaluations of denosumab for patients with bone metastases secondary to OST (not including prostate or breast cancers). Three of the four studies were industry-sponsored — two by Amgen (Stopeck et al.[9] and Lothgren et al.[10]), and one by Novartis

(Yfantopoulos et al.[8]) — and one was a study by an independent review group (Ford et al.[5]). These studies are summarized in the paragraphs that follow.

Ford et al.[5] (independent)

Ford et al.[5] undertook an HTA of denosumab for the treatment of bone metastases from solid tumours from the perspective of the UK National Health Service (NHS). The authors undertook a systematic review of the clinical effectiveness information, focusing on randomized controlled trials (RCTs) assessing denosumab, bisphosphonates, or best supportive care (BSC) in patients with bone metastases. Studies suitable for meta-analysis were synthesized using network meta-analysis (NMA). A systematic review was conducted for cost, quality of life, and cost-effectiveness studies, the results of which helped inform a cost-utility model that was amended from the manufacturer-submitted economic model. The manufacturer submitted a cost-utility Markov model over a 10-year time horizon with a cycle time of four weeks. The authors made some structural additions for their economic analysis. The model divided patients based on whether they were naive or experienced with skeletal-related events (SREs) at the start of treatment. When patients were on treatment, they could have an SRE, adverse event (AE), or discontinue; transitioning to BSC.

The primary assumption is that there is no difference in overall survival between treatments, as supported by the results of the head-to-head trial of denosumab and zoledronic acid. To include pamidronate and BSC in the analysis, an NMA was undertaken. A review of the literature identified two studies for patients with OST (with subgroups for NSCLC) that were suitable for the NMA. The results of the NMA found denosumab was effective in delaying time to first SRE and reducing the risk of multiple SREs compared with zoledronic acid; denosumab was similar to zoledronic acid for quality of life, pain, overall survival and safety; and while denosumab appeared more effective in delaying SREs than placebo, this was limited by numerous areas of uncertainties.

Cost information was informed by British National Formulary prices. A survey of oncology nurses and pharmacists indicated that denosumab would result in staff time savings compared with zoledronic acid per administration. Total annual drug costs were calculated to be £4,467 for denosumab, without a patient access scheme (PAS); £3,365 for zoledronic acid; £4,117 for disodium pamidronate; and £3,370 and £2,465 for intravenous and oral ibandronic acid, respectively. These costs do not include withheld doses due to poor renal function, or any patient management costs due to poor renal function. Costs associated with SREs and serious adverse events (SAEs) were included in the model. Costs are in £2010 (exchange rate 2010 £ to 2010 C$: £1 = C$1.5918).[16]

The model results for denosumab relative to zoledronic acid were driven by the availability of a PAS for denosumab. The manufacturer's analysis indicated that without the PAS, denosumab was not cost-effective compared with zoledronic acid (incremental cost-effectiveness ratio [ICER] above £100,000 per quality-adjusted life-year [QALY] for the SRE-experienced OST patient population; SRE-naive was compared with BSC only). With the PAS, denosumab dominated zoledronic acid.

The authors undertook substantially more reanalyses than were presented by the manufacturer (including subgroup analyses). With the PAS, the ICER improves to between £5,400 and £15,300 per QALY for OST including NSCLC and £12,700 per QALY for NSCLC. The authors reported that (with PAS) probabilistic analyses for OST including NSCLC indicate there is a 75% likelihood of denosumab being cost-effective compared with bisphosphonates at a willingness to pay (WTP) of £20,000 per QALY, and 88% likelihood at a WTP of £30,000 per QALY. For the NSCLC population, there is a 69% likelihood of

denosumab being cost-effective compared with bisphosphonates at a WTP of £20,000 per QALY, and 77% likelihood at a WTP of £30,000 per QALY.

Owing to small patient gains estimated, the cost-effectiveness of denosumab was very sensitive to the zoledronic acid price. Denosumab was not estimated to be cost-effective compared with BSC.

The authors reported that the manufacturer's model did not include subsequent SREs in the subgroup of patients SRE naive at baseline; the reason for this was not well justified. The study was limited in that only subgroup data were available for denosumab for NSCLC, and OST excluding NSCLC; the NMA was subject to numerous uncertainties (as noted in the CDR Clinical Report); and given the small patient gains estimated (in QALYs), the cost-effectiveness of denosumab was very sensitive to the zoledronic acid price. Questions also exist around patients receiving intravenous chemotherapy every three weeks, given the likelihood that any intravenous bisphosphonates would be administered every three weeks. The authors stated "whether or not denosumab would be administered on a 3-weekly basis in this situation is a moot point," but if dosed every four weeks in those patients, would likely result in denosumab being cost-saving. The authors also note that "unfortunately, the CSR [Clinical Study Report], the manufacturer's model and the submission do not provide sufficient detail to be able to present [an] analysis for the patient group of OST excluding multiple myeloma." Although there may be some potential for differences in pricing and dosing between the UK and Canadian setting, the general findings that there is little difference in effectiveness and that the results are predominantly driven by treatment costs appears to be generalizable to the Canadian setting.

Stopeck et al.[9] (Amgen-sponsored)
Stopeck et al.[9] conducted a study to determine the lifetime cost-effectiveness of denosumab versus zoledronic acid for the prevention of SREs in patients with advanced solid tumours and bone metastases from a US managed care perspective. The authors developed a lifetime Markov model, with relative rate reductions in SREs for denosumab versus zoledronic acid derived from three pivotal trials in prostate cancer, breast cancer, and NSCLC. The model was structured identically for both treatments and across all tumour types, but with treatment- and tumour-specific model inputs. The model consisted of three Markov health states: "on treatment", "off treatment", and "dead". Treatment discontinuation was incorporated into the model. While on treatment, patients experienced an SRE risk and an AE risk, disutilities associated with each, and various costs associated with SREs, AEs, and treatment; while off treatment, patients experienced an SRE risk, associated disutility, and cost. Patients cycled through health states every 28 days. The model was run for 200 cycles (15.3 years), after which 99% of patients had transitioned to the "dead" health state; more than 70% had transitioned to that state within the first four years.

Model probabilities of SRE, death, drug discontinuation, and AE were derived primarily from the results of three pivotal head-to-head phase 3 clinical trials comparing denosumab with zoledronic acid every four weeks. The model used constant rates over the lifetime of the patient, with the probabilities for each cycle calculated by assuming exponential relationships between the rates and probabilities. Real-world SRE rates in zoledronic acid–treated patients were incorporated from a large commercial database. SRE costs were estimated from a nationally representative commercial claims database. Drug, drug administration, and renal monitoring costs were included and sourced from privately held wholesalers. Assumptions were made to assess the SRE costs for NSCLC (average of SRE costs for breast cancer and prostate cancer). Costs and QALYs were discounted at 3% annually. One-way and probabilistic sensitivity analyses were conducted.

Denosumab was found to be associated with a reduction in the number of SREs compared with zoledronic acid, as well as an increase in patients' quality of life; accruing an incremental 0.06 QALYs at a cost of $4,076, resulting in an ICER of $67,931 per QALY compared with zoledronic acid for the NSCLC population (exchange rate 2011 US$ to 2011 C$: US$1 = C$0.9891).[16] The results were sensitive to drug costs, discontinuation, and SRE rates. The probabilistic sensitivity analysis indicated that there is a 60% probability of denosumab being cost-effective at a WTP of $100,000 per QALY for NSCLC, 62% for breast cancer, and 83% for prostate cancer.

The authors indicated this study is more appropriate than others as their study uses real-world data for SREs, and data from clinical trials may underestimate the expected SRE rate. Other limitations identified pertain to the inability to accurately measure certain costs (pain medications) and the impact these have, and treatment compliance. The results of this article are not likely to be transferrable to the Canadian setting, given the potential for differences in pricing, dosing, and SRE rates between US and Canadian clinical practice. While the results may not be directly generalizable to the Canadian setting, the general findings of the article — that there appears to be a very small incremental benefit for denosumab that is associated with a higher treatment cost — are comparable to other published literature and indirectly support the CDR analysis.

Lothgren et al.[10] (Amgen-sponsored)

Lothgren et al.[10] undertook a study to assess the cost implications of patients with bone metastases secondary to solid tumours transitioning from zoledronic acid to denosumab in Austria, Sweden, and Switzerland. The authors included country-specific medication, administration, and patient management costs. SRE-related costs for Austria and Sweden were obtained from a retrospective chart review of patients with bone metastases secondary to various cancer types in patients across Europe, while for Switzerland, SRE costs were calculated using Swiss inpatient and outpatient data. Real-world data informed the frequency of administration of zoledronic acid, while data from the head-to-head trial of denosumab and zoledronic acid were used to provide SRE rates for zoledronic acid and denosumab. The authors presented the results stratified by breast cancer, prostate cancer, and OST.

The authors reported that in all countries, transitioning from zoledronic acid to denosumab in a patient with bone metastases secondary to OST was cost-saving, ranging from €1,861 (Austria) to €3,408 (Switzerland) per patient, per year (exchange rate 2012 € to 2012 C$: €1 = C$1.2850).[16] Cost savings were driven by a delay in time to SREs, lower SRE-related costs, and lower administration costs for denosumab. Cost savings differed between indications and country based on transition rates, SRE costs, and administration costs. The results were robust to sensitivity analyses, with price reductions of up to 80% required for zoledronic acid to be cost-saving.

The following limitations were identified: the use of trial-based SRE rates, which may be an underestimate compared with the real-world SRE rate; the real-world administration data used were not based on country-specific data; and the short time horizon may not represent the total value for denosumab.

Given the potential for differences in pricing and dosing between Dutch and Canadian settings, and — as the authors noted — contrasting costs and quality of life were not in the scope of the study, the results of this article are not likely to be transferrable to the Canadian setting.

Yfantopoulos et al.[8] (Novartis-sponsored)

Yfantopoulos et al.[8] undertook a study of denosumab versus zoledronic acid for patients with bone metastases secondary to solid tumours from a third-party payer perspective in Greece. The authors stratified the population to three cancer types: breast cancer, prostate cancer, and OST. The authors reported that they adapted an Excel-based model developed by Lothgren et al. for the same population in the Dutch setting. The authors reported using the same efficacy and quality of life data as Lothgren et al., but using health care cost and resource utilization from the Greek health care system; however, it should be noted that Yfantopoulos et al. were referring to a model that was presented only in abstract form. The authors included only direct medical costs (including drug acquisition, administration, SREs, and patient monitoring). The authors conducted the analyses for the three separate populations over different time horizons: 22.5 months for breast cancer, 14.5 months for prostate cancer, and nine months for OST.

The authors reported that most of the clinical data were the same as those used in the study by Lothgren et al. and that this information had been sourced from phase 3 clinical trials. Discontinuation rates were sourced from published literature. Health care and resource utilization costs were sourced from Greek Ministry of Health and pharmacy costs, published Greek costs, and government bulletins.

The authors reported their results based on three different scenarios: 1) denosumab is obtained and reimbursed as a hospital-administered therapy, 2) denosumab is assumed to be obtained from community pharmacists for subsequent injections except for the first one, and 3) zoledronic acid is available at generic prices following patent expiration in 2013. Scenarios 1 and 3 appeared to report the same incremental QALY values (0.0046 to 0.005; difference in rounding), while the incremental QALYs for scenario 2 were not reported, but based on the scenario description, were expected to be the same as scenarios 1 and 3. Based on scenario 1, the base-case analysis resulted in an incremental cost per QALY of €56,818 for breast cancer, €61,296 for prostate cancer, and €80,830 for OST (exchange rate 2012 € to 2012 C$: €1 = C$1.2850).[16] In scenario 2, results indicated that the incremental cost per QALY was above €100,000 per QALY for all indications (range: €112,414 to €163,993) with OST representing the least cost-effective indication, while the same situation was apparent with scenario 3 with higher ICERs (range: €198,431 to €328,364).

The authors found that although denosumab was more efficacious, the associated incremental costs meant that denosumab was not considered a cost-effective alternative to zoledronic acid. The authors noted limitations with the use of clinical trial data and the difference with “real-life” data, as well as the assumption that the clinical inputs and structure of the model in the Lothgren et al. study was applicable to the Greek setting.

The results of this article are not likely to be transferrable to the Canadian setting, given the potential for differences in pricing and dosing between the Greek and Canadian settings.

APPENDIX 4: PUBLISHED HEALTH TECHNOLOGY ASSESSMENT REPORTS

TABLE 4: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	NICE (October 2012)	NCPE (December 2011)
Treatment	denosumab (Xgeva) 120 mg/1.7 mL	
Price	£309.86/vial; £4,028.18/year – excl. VAT	Not stated
Population/s	Prevention of SREs in adults with bone mets from solid tumours (sub pops: BC, PC, and OST incl. NSCLC).	Treatment of SREs in adults with bone mets from solid tumours (specifically BC, PC, and OST excluding MM).
Comparators	BSC (on prior SRE), and ZA and disodium pamidronate (prior SRE).	Primary comparator was ZA.
Similarities with CDR submission	Model structure similar to INESSS (thus CDR). Markov model had 5 health states: no prior SREs (on tx/off tx), prior SREs (on tx/off tx), and death. Model cycle was 4 weeks.	A Markov cohort model was used, though the model structure was not reported. The primary comparator was ZA.
Differences with CDR submission	TH = 10 years. Included BSC and ibandronic acid as comparators. Canadian clinical practice differs from UK. Treatment costs are UK-specific.	Clinical outcomes for OST from Henry 2010. TH = 10 years. Discount rate = 4% (costs, consequences). Canada's clinical practice differs from Ireland's.
Manufacturer's results	*Base case:* incr cost £757, incr QALY 0.004, ICER £205,580 vs. ZA.[a] Dominated disodium pamidronate.[a] *No prior SRE:* incr cost £2,530, incr QALY 0.021, ICER of £122,499 vs. BSC.[a]	Denosumab dominated ZA.
Issues noted by the review group	Assessment Group: rebuilt manufacturer's model using same basic structure, but included separate NSCLC analysis; made amendments to resource data; revised drug prices, event and SAE costs.	Review group modelled alternative scenario revising drug costs for denosumab and ZA, admin costs for denosumab under HTD scheme, admin costs for ZA, and relative SRE rate of denosumab vs ZA.
Results of reanalyses by the review group (if any)	*Base case:* incr cost £848, incr QALY 0.004, ICER £196,114 vs. ZA.[b] *No prior SRE:* incr cost £2,473, incr QALY 0.024, ICER £103,350 vs. BSC.[b] Assessment Group SA to assess alternative discontinuation rates, utility changes and multipliers, excluding SAEs, TH (5-yr, 2-yr), extend effect of spinal cord	In the alternative scenario the probability of denosumab being cost-effective at a willingness-to-pay threshold of €20,000 per QALY gained was 38.9% in the prostate cancer model, 46.9% in the breast cancer model and 52.1% for all other tumours.

	NICE (October 2012)	NCPE (December 2011)
	compression beyond 5 m, alternative drug costs. Results generally supported base-case.	
Recommendation	Committee recommended denosumab for preventing SREs in adults with bone mets from BC and OST (other than PC), if mfr provided agreed-upon discount in PAS.	Denosumab may be considered cost-effective therapy for prevention of SREs in adults with bone mets from solid tumours.

BC = breast cancer; BSC = best supportive care; CDR = CADTH Common Drug Review; HTA = health technology assessment; HTD = High Tech Drugs; incr = incremental; ICER = incremental cost-effectiveness ratio ($/QALY); mfr = manufacturer; INESSS = Institut national d'excellence en santé et en services sociaux; MM = multiple myeloma; NCPE = National Centre for Pharmacoeconomics (Ireland); NICE = National Institute for Health and Care Excellence (UK); NSCLC = non–small cell lung cancer; OST = other solid tumours; PAS = patient access scheme; PC = prostate cancer; QALY = quality-adjusted life-year; SA = sensitivity analysis; SAE = serious adverse event; SRE = skeletal-related event; TH = time horizon; VAT = value-added tax; ZA = zoledronic acid.

[a] All analyses presented without PAS.

[b] All analyses presented without PAS. Results with PAS found denosumab dominated ZA, disodium pamidronate, and ibandronic acid in all indications. The ICER for denosumab compared to BSC was £83,763/QALY for OST.

Note: Currency conversion rates (2010 £ to 2010 C$): 1£ = C$1.5918. http://www.bankofcanada.ca/rates/exchange/annual-average-exchange-rates/ [accessed November 2, 2015]

APPENDIX 5: OTHER POTENTIAL COMPARATOR TREATMENTS

TABLE 5: OTHER POTENTIAL TREATMENTS FOR PATIENTS WITH BONE METASTASES WITH OTHER SOLID TUMOURS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Other bisphosphonates that may be used					
Alendronate (generic)	70 mg 10 mg	Tablet	2.5144 0.4987	70 mg weekly or 10 mg daily	131 to 182
Alendronate/ cholecalciferol (generics)	70 mg/70 mcg 70 mg/140 mcg	Tablet	2.3312 3.4969	One tablet once weekly	122 to 182
Etidronate disodium	200 mg	Tablet	0.3569	2 tablets daily	261
Etidronate and calcium carbonate (generic)	400 mg and 500 mg	Tablet	19.9900[a]	90-day treatment cycle: 1 tablet etidronate for 14 days, then 1 tablet calcium for 76 days	81
Risedronate sodium (generic)	150 mg 35 mg 30 mg 5 mg	Tablet	11.1875 2.4893 8.8500 1.3661	35 mg weekly 5 mg daily 150 mg monthly	130 to 499
Zoledronic acid (Aclasta generics)	5 mg/100 mL	Infusion	335.4000	Once yearly	335

[a] 90-tablet kit.
Source: Ontario Drug Benefit (effective August 2015) prices unless otherwise stated.

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