Common Drug Review
Pharmacoeconomic Review Report

February 2016

Drug	denosumab (Xgeva)
Indication	For reducing 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	For reducing the risk of developing skeletal-related events in patients with bone metastases from breast cancer
Dosage Form(s)	120 mg/1.7 mL single-use vial solution for injection
NOC Date	May 10, 2011
Manufacturer	Amgen Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
BSC	best supportive care
CDR	CADTH Common Drug Review
FWG	Formulary Working Group
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
INESSS	Institut national d'excellence en santé et en services sociaux
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSCLC	non–small cell lung cancer
OST	other solid tumours
PAS	patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
QALY	quality-adjusted life-year
RAMQ	Régie de l'assurance maladie du Québec
RCT	randomized controlled trial
SRE	skeletal-related event
WTP	willingness-to-pay

SUMMARY OF THE ECONOMIC INFORMATION

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 provided an electronic copy of the economic model and report submitted to Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) for the breast cancer indication; sections C and D of the submission to Australia's PBAC for the breast cancer and prostate cancer indications; the report submitted to the National Institute for Health and Care Excellence (NICE) for the full indication (breast cancer, prostate cancer, and other solid tumours [OST]); and a document outlining the differences between the UK, Australian, and Canadian models.

Drug Product	Denosumab (Xgeva)
Study Question	Estimate the cost-effectiveness of denosumab relative to zoledronic acid in the treatment of advanced breast cancer patients with bone metastases, from the Quebec societal perspective. A scenario analysis also considered denosumab relative to pamidronate.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with bone metastases secondary to breast cancer
Treatment	Denosumab (Xgeva) 120 mg/1.7 mL
Outcome	QALYs
Comparators	• Zoledronic acid • Pamidronate (scenario analysis)
Perspective	Health care payer
Time Horizon	Lifetime (model stopped at 15 years)
Results for Base Case	• Denosumab dominated zoledronic acid • Denosumab dominated pamidronate (scenario analysis)
Key Modifications Required	Use drug and related administration and monitoring costs from provinces participating in the CDR process
Key Limitations/ Revisions	• Uncertainty of generalizability of SREs to current Canadian practice • Uncertainty regarding SRE costs • Comparative efficacy of pamidronate underestimated • Time horizon is overestimated • Calculation of disutility values
CDR Estimates	• CDR analyses found the ICURs of denosumab compared with zoledronic acid or pamidronate were greater than $395,000 per QALY assuming the manufacturer funds the infusion costs. • If the province funds infusion costs, the ICURs for denosumab vs. zoledronic acid or pamidronate are still greater than $195,000 per QALY. • Several limitations could not be assessed, including uncertainty around the way SREs are modelled and costed, the time horizon, and the comparison of denosumab with clodronate. • CDR did not undertake reanalyses based on clinical data from an indirect comparison of denosumab with pamidronate. • The results of CDR analyses are supported by the published literature.

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SRE = skeletal-related event; vs. = versus.

EXECUTIVE SUMMARY

Background

Denosumab (Xgeva) is being reviewed for the patient population with bone metastases secondary to breast cancer. CADTH Common Drug Review (CDR) undertook a concurrent review for patients with bone metastases from non–small cell lung cancer (NSCLC) and other solid tumours (OST).

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

Denosumab (Xgeva) has previously been reviewed by the CADTH 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 bone metastases and good performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of 0 to 2), in jurisdictions that list 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 CDR program. The manufacturer of denosumab was invited to submit clinical and/or economic information but was not obligated to do so. The manufacturer provided an electronic copy of the economic model and report submitted to Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) for the breast cancer indication; sections C and D of the submission to Australia's Pharmaceutical Benefits Advisory Committee (PBAC) for the breast cancer and prostate cancer indications; the report submitted to the National Institute for Health and Care Excellence (NICE) for the full indication (breast cancer, prostate cancer, and OST); and a document outlining the differences between the UK, Australian, and Canadian models.

CDR reviewed the materials provided by the manufacturer and determined that the economic model submitted to INESSS would be relevant as the base model for the review, though inputs would need to be altered to make it applicable to CDR-participating drug plans. The document provided by the manufacturer regarding the differences between the Australian model, UK, and Canadian models meant that data from the Australian submission was not included within the CDR review (the PBAC Public Summary Document was summarized in Appendix 2). As the information provided was not tailored to the CDR setting, CDR also undertook a review of the published literature to supplement the evidence provided.

Model Revisions and Key Results

As the model was based on a submission to INESSS and the Quebec setting, CDR identified two initial modifications that were required based on the different setting and perspective:

- **Revisions of drug costs based on prices from participating drug plans.** CDR updated the model provided using data from the Ontario Drug Benefit Formulary[1,3] where possible and the Alberta Blue Cross Formulary[4] where Ontario prices were not available.
- **Revisions to health care resource use costs.** CDR updated the model provided using data from the Ontario Schedule of Benefits.[5]

Aside from the initial jurisdictional cost differences, CDR identified several aspects within the information and model provided by the manufacturer that limit what can be determined regarding the cost-effectiveness of denosumab in this population. The limitations are summarized as follows:

- **Uncertainty of generalizability of SREs in the clinical study to current Canadian practice.** The CDR clinical expert reported that the low pain score in the pivotal trial (Breast Cancer Study 136) does not coalesce with the high proportion of patients with SREs (particularly radiation to the bone), which may indicate differences between the studied population and current Canadian practice. There is some uncertainty as to how events were coded to avoid double-counting (e.g., pathologic fracture leading to radiation to the bone, surgery).
- **Uncertainty around modelling and calculation of SRE values.** There is uncertainty as to whether events were coded to avoid double-counting of costs (as noted above), as well as utility decrements (i.e., pathologic fracture may lead to patient receiving radiation of the bone). The aggregation of costs and disutility values for the four SREs (surgery to bone, radiation to bone, spinal cord compression, and pathologic fracture of the bone) may not be appropriate given the differences between the individual utility values and costs, and potential differences in the timing of events.
- **Uncertainty regarding SRE costs.** The SRE costs in the model provided by the manufacturer were not well described, were not able to be verified by CDR, and may be dated. The results were based on patients with a wide range of cancers, and the type of cancer may have an impact on the associated resource utilization and cost.
- **Comparative efficacy of denosumab versus pamidronate or clodronate is uncertain.** CDR clinical reviewers found the results of the indirect treatment comparison indicated denosumab was at least as effective as pamidronate, although these findings are associated with a high degree of uncertainty. As superiority over pamidronate was not proven, a cost analysis or cost-minimization analysis may have been more appropriate. No published literature was identified to assess the comparative efficacy of denosumab and clodronate, thus comparative efficacy is uncertain.
- **Time horizon may be too long given the patient population.** The CDR clinical expert indicated that the lifetime time horizon presented by the manufacturer (15 years) was longer than is likely to occur in clinical practice.

Using the economic model provided by the manufacturer, CDR considered prices and costs from CDR-participating plans, including drug and administration costs (including expert visits), to determine a base case applicable to the CDR setting. The base case results were presented based on infusion costs being funded by the manufacturer. In the base case, the incremental cost-utility ratios (ICURs) for denosumab compared individually with zoledronic acid (approximately $700,000 per quality-adjusted life-year [QALY]) or pamidronate (approximately $400,000 per QALY) were high and uncertain. When adjusting for a shorter (trial-based) time horizon, the ICURs increased slightly but generally remained stable. A sensitivity analysis assessing the impact of the province funding infusion costs indicated that the ICUR for denosumab was still above $195,000 per QALY at the lowest value. Due to the uncertainty with the clinical data and modelling of events in a model not constructed for a submission to CDR, CDR did not test the impact of the other limitations identified with the economic model. A price reduction of between 60% and 75% was required for denosumab to dominate (i.e. be more effective, less costly than) zoledronic acid based on the CDR base case analysis.

Conclusions

Based on the CDR analyses, at the list price of denosumab ($575.55 per 120 mg pre-filled syringe in Ontario), and the list price for generic zoledronic acid ($38.79 per 0.8 mg/mL injection in Alberta) and generic pamidronate ($3.03 to $9.10 depending on strength, in Alberta), the ICUR for denosumab compared individually with zoledronic acid or pamidronate was greater than $395,000 per QALY where the manufacturer funds the infusion cost. For plans that fund the infusion cost, the ICUR would fall, but would still be greater than $195,000 per QALY. The results of CDR reanalyses are generally supported by published literature.

REVIEW OF THE PHARMACOECONOMIC INFORMATION

1. SUMMARY OF THE PHARMACOECONOMIC INFORMATION PROVIDED BY THE MANUFACTURER

CADTH Common Drug Review (CDR) appraised the information provided by the manufacturer including the cost-utility analysis (CUA) report and Markov model comparing denosumab (Xgeva) primarily with zoledronic acid for advanced breast cancer patients with bone metastases over a lifetime time horizon that was submitted to the Institut national d'excellence en santé et en services sociaux (INESSS). The CUA was undertaken from multiple perspectives, including the health care payer perspective, and presented a scenario analysis comparing denosumab with pamidronate for the same indication.

In the Markov model provided by the manufacturer, patients enter the model at age 57 years, and transition through three health states in the model: "on treatment", "off treatment", and "dead". The risk of an SRE was included for patients on and off treatment (Figure 1). Treatment-emergent adverse events (AEs) were included in the "on treatment" health state. Although a lifetime time horizon was reported to be used, it was noted the model was stopped after 15 years as 99% of patients had transitioned to the "dead" health state. Patients cycled through health states every four weeks.

Transition probabilities for denosumab and zoledronic acid for treatment discontinuation, incidence of AEs and efficacy were obtained from a head-to-head clinical trial of advanced breast cancer patients with bone metastases (Breast Cancer Study 136).[6] Data for pamidronate was informed from an indirect treatment comparison.[7,8] Utility data were obtained directly from Breast Cancer Study 136.[6]

Costs and resource use were sourced from the published literature, Régie de l'assurance maladie du Québec (RAMQ),[9] the Ontario Case Costing Initiative, input from a physician panel, and a Canadian retrospective chart review. The submitted drug acquisition cost of denosumab was based on price parity with the acquisition cost of zoledronic acid. Costs were reported in 2011 Canadian dollars. Generic zoledronic acid was not available at the time of analysis.

2. MANUFACTURER'S BASE CASE

The manufacturer's submission to INESSS reported that in the population with advanced breast cancer patients with bone metastases, based on the probabilistic model with 2,000 iterations, denosumab dominated (i.e. was more effective and less costly than) both zoledronic acid and pamidronate. Deterministic and probabilistic sensitivity analyses supported these results.

3. REVISIONS TO THE SUBMITTED ECONOMIC EVALUATION

The model was populated based on a submission to INESSS and its specific setting, thus CDR identified two modifications that were required based on the different setting and perspective:

- **Revision of drug costs based on prices from participating drug plans.** CDR updated the model using data from the Ontario Drug Benefit Formulary (ODBF) where possible and the Alberta Blue Cross Formulary where Ontario prices were not available. The price of denosumab on the ODBF is higher than the price submitted to INESSS, while the price of zoledronic acid on the Alberta Drug Formulary

is lower than the price in the submitted model. The price of clodronate and denosumab were sourced from the Ontario Drug Benefit Formulary[3] and Exceptional Access Program[1] respectively, while the prices for zoledronic acid (Zometa) and pamidronate were sourced from the Albert Blue Cross Formulary[4] because as of November 2015, neither province listed all four treatments.

- **Revision of health care resource use costs to those used by participating drug plans.** CDR updated the model using data from the Ontario Schedule of Medical Benefits. The cost of a specialist visit in Ontario is slightly higher than the cost input from Quebec that populated the model that was provided.

CDR identified several limitations with the structure of the model, as well as data used in the model. These limitations are summarized as follows:

- **Uncertainty of generalizability of SREs in the clinical study to current Canadian practice.** The CDR clinical expert noted the mean pain score in the trial (Brief Pain Inventory [Short Form] [BPI-SF] score of 2.5) is lower than seen in practice, and that patients with a pain score of 2 or less are generally not treated with radiation therapy. Therefore, the proportion of patients requiring radiation therapy may be lower in Canadian clinical practice than occurred in the trial. The CDR clinical expert reported that the proportion of patients with skeletal-related events (SREs) appears to be higher than expected. The study does not provide clarity as to how events were coded to ensure there is no double-counting of events (e.g., pathologic fracture leading to radiation to the bone, surgery), which may explain the high SRE proportion and lead to double-counting of costs.[6] The CDR Clinical Report indicates that any subsequent event had to occur 21 days or more after the previous SRE to ensure potentially related events (such as surgical procedures for a fracture) were not counted as separate events; however, there is still some ambiguity as to how these patients were coded.
- **Uncertainty around modelling and calculation of SRE values.** It is unclear whether there is double-counting of costs and utility decrements (pathologic fracture leading to radiation of the bone). The model aggregates costs and disutility values for the four SREs (surgery to bone, radiation to bone, spinal cord compression, and pathologic fracture of the bone), which may not be appropriate given large differences between individual utility values and costs, and potential differences in the timing of events.
- **Uncertainty regarding SRE costs.** SRE costs were reported to have been based on a Canadian retrospective review of medical records conducted at two sites in Quebec and Ontario, but were not well reported. The information provided on this study did not indicate the individual cost areas used to determine the eventual costs associated with each SRE. The SRE costs were reportedly based on 172 patients with varying cancer types, and not stratified by cancer type. It is uncertain as to whether this appropriately represents the resource utilization associated with SREs for a patient with breast cancer.
- **Comparative efficacy of denosumab versus pamidronate or clodronate is uncertain.** CDR clinical reviewers reported the results of the indirect treatment comparison indicated denosumab is at least as effective as pamidronate for reducing the risk of a first SRE in patients with advanced breast cancer and bone metastases, although these findings are associated with a high degree of uncertainty. These findings call into question the assumption of superior effectiveness used in the economic model. If equal effectiveness was assumed, a cost analysis or cost-minimization analysis would be more appropriate. No clinical comparison of denosumab to pamidronate or clodronate was identified; therefore the comparative efficacy is uncertain.

- **Time horizon may be too long given the patient population.** The CDR clinical expert indicated that the time horizon presented by the manufacturer (15 years) was longer than is likely to occur in Canadian clinical practice in the vast majority of patients with bone metastases with breast cancer.

4. ISSUES FOR CONSIDERATION

CDR identified the following issues for consideration:

- The appropriate comparator for denosumab differs between jurisdictions 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.

As this submission was at the request of the Formulary Working Group (FWG), there was limited directly applicable information for the economic review. While the manufacturer provided information from its submission to INESSS, the information was specific to that submission and full details were not provided (as it was not a requirement). Several inputs in the model could not be verified by CDR. For example, the intercept, scale, and shape used in to the model to assist in modelling survival were stated to be included in the Clinical Study Report, but were not included in the material provided to CDR.

5. CADTH COMMON DRUG REVIEW ANALYSES

CDR undertook an analysis using prices and costs from CDR-participating plans, assuming that infusion costs are funded by the manufacturer, to determine a base case applicable to the CDR setting (Table 1). The generic prices of zoledronic acid and pamidronate were used.

TABLE 1: CADTH COMMON DRUG REVIEW BASE-CASE ANALYSIS

Parameter	QALYs	Costs	ICUR
Denosumab Versus Zoledronic Acid			
Drug and administration costs based on jurisdictions participating in the CDR process (manufacturer funds infusion cost)	0.0111	$7,868	$709,153/QALY
Denosumab Versus Pamidronate			
Drug and administration costs based on jurisdictions participating in the CDR process (manufacturer funds infusion cost)	0.0238	$9,477	$397,555/QALY

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

CDR was unable to test several of the identified limitations, including coding of SREs, SRE costs, verifiability, and comparative efficacy of denosumab and pamidronate. CDR was able to test the impact of a shorter time horizon and infusion cost, individually and in combination, on the results (Table 2).

TABLE 2: CADTH COMMON DRUG REVIEW SENSITIVITY ANALYSES ($/QALY)

Parameter	ICUR (Denosumab Versus Zoledronic Acid)	ICUR (Denosumab Versus Pamidronate)
Trial-based time horizon (28 months)	$738,848	$404,752
Infusion funded by province	$376,094	$197,475
Shorter time horizon and infusion funded by province	$390,971	$200,626

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

As noted in the limitations, there is uncertainty with the degree of comparative clinical efficacy for denosumab compared with zoledronic acid, pamidronate, and clodronate. The small incremental quality-adjusted life-year (QALY) difference reported by the model highlights substantial volatility in the model results. CDR considers the results of the reanalysis to be high and uncertain.

5.1 Price Reduction Analysis

CDR undertook a price reduction analysis on the CDR base case, which indicated that a price reduction of between 60% and 75% is required for denosumab to dominate the primary comparators (Table 3).

TABLE 3: CADTH COMMON DRUG REVIEW PRICE REDUCTION SCENARIOS

ICURs of Denosumab for the Base Cases			
Price of Denosumab	Manufacturer Analysis of Denosumab Versus ZA and Pamidronate[a]	CDR Analysis	
		Denosumab Versus Generic ZA	Denosumab Versus Generic Pamidronate
Ontario ($575.55)	Dominant	$709,153/QALY	$397,555/QALY
10% reduction ($518.00)	Dominant	$588,345/QALY	$341,329/QALY
15% reduction ($489.22)		$527,941/QALY	$313,216/QALY
20% reduction ($460.44)		$467,537/QALY	$285,103/QALY
25% reduction ($431.66)		$407,133/QALY	$256,990/QALY
30% reduction ($402.89)		$346,729/QALY	$228,877/QALY
35% reduction ($374.11)		$286,325/QALY	$200,764/QALY
40% reduction ($345.33)		$225,921/QALY	$172,651/QALY
45% reduction ($316.55)		$165,518/QALY	$144,538/QALY
50% reduction ($287.87)		$105,114/QALY	$116,425/QALY
55% reduction ($259.00)		$44,710/QALY	$88,312/QALY
60% reduction ($230.22)		Dominant	$60,200/QALY
65% reduction ($201.44)			$32,087/QALY
70% reduction ($172.67)			$3,974/QALY
75% reduction ($143.89)			Dominant

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; ZA = zoledronic acid.
[a] In the analysis provided by manufacturer, denosumab is dominant using the submitted INESSS price and listed Ontario price.

A price reduction scenario based on the sensitivity analysis considering the assumption that provinces fund the infusion costs is presented in Appendix 5 (Table 10).

6. SUMMARY OF THE PUBLISHED LITERATURE

As no formal submission to CDR was presented, CDR undertook a review of the published economic studies of denosumab for patients with bone metastases secondary to breast cancer to determine whether any information may be useful to inform the review.

The full details of the review are provided in Appendix 4: Review of the Published Literature. Six relevant economic evaluations were identified; five of the six studies were industry-sponsored — two by Amgen (Stopeck et al.[10] and Lothgren et al.[11]) and three by Novartis (Yfantopoulos et al.,[12] Snedecor et al.,[13] and Xie et al.[14]) — and one was a study by an independent review group (Ford et al.[15]).

In all of the studies, the primary comparator for denosumab was zoledronic acid. One study (Lothgren et al.)[11] was a European budget impact assessment based on a patient switching from zoledronic acid to denosumab, while the other five 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 incremental cost-effectiveness ratios (ICERs) ranged from denosumab being dominant where a patient access scheme was in place (essentially a reduced price)[15] to €380,000 per QALY (exchange rate 2012 € to 2012 C$: €1 = C$1.2850)[16] for denosumab compared with zoledronic acid.[12] Without a patient access scheme in place, the ICER was assessed to be greater than £200,000 per QALY[15] (exchange rate 2010 £ to 2012 C$: £1 = C$1.5918).[16] Common to each of these studies, at a willingness-to-pay (WTP) threshold of $50,000 per QALY or per SRE avoided, denosumab was not cost-effective. These findings are aligned with the results obtained from the manufacturer's economic model.

7. PATIENT INPUT

Input was received from three patient groups: the Canadian Cancer Survivor Network, Canadian Breast Cancer Network, and Rethink Breast Cancer. The input was independently prepared and submitted. Information was gathered from a variety of sources, including surveys, a literature review, a face-to-face interview, and five online/telephone interviews. Participants in the surveys reported the most difficult physical consequences from bone metastases to control were bone pain, weakness, fracture, sleeping problems/insomnia, and spinal compression. Managing pain symptoms and movement loss is critical to improve patients' quality of life, as patients were reported to understand impact of treatments on survival and seek to live remaining months or years with the best quality of life possible. Patients reported that the consequences of bone metastases place significant restrictions on activities such as work, caring for children, and engaging in family and social gatherings. Patients reported having difficulties with affording the cost of medications, as many were self-employed; other treatment options were reported to have time and travel costs as well as significant or debilitating impact on quality of life.

Patients reported that current treatments such as zoledronic acid and pamidronate were associated with severe flu-like symptoms and renal complications, which may become intolerable, thus new alternatives with fewer AEs are desired.

8. CONCLUSIONS

The economic information provided by the manufacturer was based on a submission to INESSS. CDR reviewed the information and attempted to increase the applicability to participating plans.

Based on the CDR analyses, at the list price of denosumab ($575.55 per 120 mg pre-filled syringe in Ontario), and the list price for generic zoledronic acid ($38.79 per 0.8 mg/mL injection in Alberta) and generic pamidronate in Alberta ($3.03 to $9.10 depending on strength, in Alberta),[1] CDR found denosumab to be associated with slightly more QALYs but higher total costs, with the resulting incremental cost-utility ratio (ICUR) for denosumab compared individually with zoledronic acid or pamidronate greater than $395,000 per QALY where the manufacturer funds the infusion cost. Were the province to fund the infusion cost, the ICUR would be reduced, but still greater than $195,000 per QALY. The small incremental QALY difference highlights substantial volatility in the model results. CDR identified clinical limitations associated with a substantial amount of uncertainty. The results of CDR reanalyses are generally supported by published literature.

[1] Although zoledronic acid (Aclasta) is listed on the Ontario Drug Benefit formulary,[3] Zometa (comparator of interest) does not have a listed price there or on the Exceptional Access Program; the same is true of pamidronate. Thus, both comparator prices have been sourced from the Alberta Blue Cross Formulary.[4] The prices of generic and branded zoledronic acid differ substantially between Alberta and BC.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 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. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 4: CADTH COMMON DRUG REVIEW COST COMPARISON TABLE FOR DENOSUMAB FOR TREATMENT OF BONE METASTASES IN PATIENTS WITH BREAST CANCER

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	1,764 to 2,646
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 (October 2015).[4] 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)[3] prices unless otherwise stated.

Appendix 6 presents a supplemental list of potential comparators.

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 2: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DENOSUMAB (XGEVA)

TABLE 5: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	NCPE (December 2011)[19]	PBAC (July 2011)[a,20]	NICE (October 2012)[21]
Treatment	**Denosumab (Xgeva) 120 mg/1.7 mL**		
Price	Price not stated.	Price not stated	£309.86 / vial (excl. VAT) £4,028.18 / year (excl. VAT)
Population/s	Treatment of SREs in adults with bone mets from solid tumours (specifically BC, PC, and OST excluding MM).	Treatment of bone mets from BC and PC	Prevention of SREs in adults with bone mets from solid tumours (sub pops: BC, PC, and OST incl. NSCLC).
Comparator/s	Primary comparator was zoledronic acid.	Primary comparator was zoledronic acid	**BC:** ZA (primary), disodium pamidronate and ibandronic acid (secondary). **PC:** BSC (on prior SRE) and ZA (prior SRE). **OST:** BSC (on prior SRE), and ZA and disodium pamidronate (prior SRE).
Similarities with CDR submission	A Markov cohort model was used, though model structure was not reported. The primary comparator was ZA.	Model cycle was 4 weeks	The structure model appears similar to that submitted to INESSS (thus to CDR). The 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 wks.
Differences with CDR submission	Clinical outcomes for OST from Henry (2010). TH = 10 years Discount rate = 4% (costs, consequences) Canadian clinical practice differs from Ireland.	Model structure appears to differ. Markov model with 3 HS: alive w/o SRE on tx, alive w/ SRE on tx, and dead. Submission did not seek listing for OST (incl. NSCLC). Model TH was 10 yrs. Clinical practice differs between Australia and Canada.	The model TH was 10 years. The model included BSC and ibandronic acid as comparators. Clinical practice differs between UK and Canada. Treatment costs are UK-specific.
Manufacturer's results	The ICUR for denosumab vs. ZA was €14,626 per QALY in the breast cancer population.	Denosumab dominated ZA.	All analyses presented without PAS[b] (ICER: $/QALY): • **BC:** *Base case:* incr cost £1,484, incr QALY gain 0.007, thus ICER £203,387 vs. ZA. ICER £13,835 vs. ibandronic acid; dominated pamidronate.

	NCPE (December 2011)[19]	PBAC (July 2011)[a,20]	NICE (October 2012)[21]
			• **PC:** Base case: incr cost £922, incr QALY gain 0.006, thus ICER £157,276 vs. ZA. *No prior SRE:* incr cost £3,993, incr QALY gain 0.039, thus ICER £102,067 vs. BSC. • **OST:** *base case:* incr cost £757, incr QALY gain 0.004, thus ICER £205,580 vs. ZA. Dominated disodium pamidronate. *No prior SRE:* incr cost £2,530, incr QALY gain 0.021, thus ICER of £122,499 vs. BSC.
Issues noted by the review group	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.		Assessment Group rebuilt manufacturer's model using same basic structure, but included separate NSCLC analysis. Assessment Group made amendments to resource data, revised drug prices, revised event costs, SAE costs.
Results of reanalyses by the review group (if any)	In the alternative scenario the probability of denosumab being cost-effective at a WTP 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.	Denosumab remained dominant with 50% of base case IV admin costs. As the assumed admin costs were lowered, the ICER increased. Using the lowest cost tested in SA, the ICER for denosumab was $100,000 to $200,000/QALY for both BC and PC.	All analyses presented without PAS (ICER: $/QALY): • **BC:** *Base case:* incr cost £1,707, incr QALY gain 0.007, thus ICER £245,264 vs. ZA; £229,547 vs. BSC; dominated pamidronate. • **PC:** *Base case:* incr cost £1,053, incr QALY gain 0.006, thus ICER £170,854 vs. ZA. *No prior SRE:* incr cost £3,969, incr QALY gain 0.039, thus ICER £103,003 vs. BSC. • **OST:** *base case:* incr cost £848, incr QALY gain 0.004, thus ICER £196,114 vs. ZA. *No prior SRE:* incr cost £2,473, incr QALY gain 0.024, thus ICER £103,350 vs. BSC. • **NSCLC:** *base case:* incr cost £708, incr QALY gain 0.005, thus ICER £149,878 vs. ZA. *No prior SRE:* incr cost £2,262, incr QALY gain 0.012, thus ICER £191,412 vs. BSC. Assessment Group performed univariate SA to assess impact of using alternative discontinuation rates, utility changes, utility multipliers, excluding SAEs, shortened time horizon (5 yr, 2 yr), extend effect of spinal cord compression beyond 5m, alternative drug costs. Results generally supported base-case conclusions.

	NCPE (December 2011)[19]	PBAC (July 2011)[a,20]	NICE (October 2012)[21]
Recommendation	Denosumab may be considered cost-effective therapy for prevention of SREs in adults with bone mets from solid tumours (full population considered).	PBAC recommended denosumab be listed for treatment of bone mets from BC and hormone-resistant PC on the basis of acceptable CE vs. ZA (4 mg/5 mL)	Committee recommended denosumab for preventing SREs in adults with bone mets from BC and OSTs (other than PC), if the manufacturer provided the agreed-upon discount in the PAS. Committee did not recommend denosumab for preventing SREs in adults with bone mets from PC.

BC = breast cancer; BSC = best supportive care; CDR = CADTH Common Drug Review; CE = cost-effectiveness; excl. = excluding; HS = health states; HTA = health technology assessment; HTD = high tech drugs; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; incl. = including; incr = incremental; INESSS = l'Institut national d'excellence en santé et en services sociaux; IV = intravenous; mets = metastases; 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; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PC = prostate cancer; QALY = quality-adjusted life-year; QC = Quebec; SA = sensitivity analysis; SAE = serious adverse event; SRE = skeletal-related event; sub pops = subpopulations; TH = time horizon; tx = treatment; UK = United Kingdom; VAT = value-added tax; vs. = versus; w/ = with; wks = weeks; w/o = without; WTP = willingness-to-pay; yr = year; ZA = zoledronic acid.

[a] PBAC meeting date listed. Date of publication not reported.

[b] Results with PAS found denosumab dominated ZA, disodium pamidronate, and ibandronic acid in all indications. With the PAS, the ICER for denosumab compared with BSC was £71,320/QALY for PC and £83,763/QALY for OST.[21]

APPENDIX 3: REVIEWER WORKSHEETS

Manufacturer's Model Structure

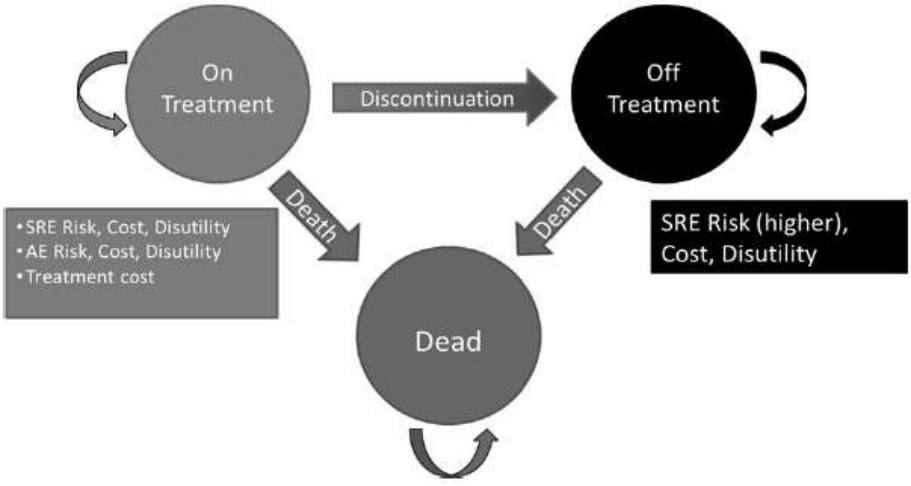
The manufacturer provided information that included a copy of the economic model and report submitted to the Institut national d'excellence en santé et en services sociaux (INESSS) for breast cancer and prostate cancer. The manufacturer also presented information from the Xgeva submission to Australia's Pharmaceutical Benefits Advisory Committee (PBAC) for breast cancer and prostate cancer, the Xgeva submission to the National Institute for Health and Care Excellence (NICE) for the full indication (breast cancer, prostate cancer, and other solid tumours [OST]). The manufacturer also presented a document outlining the differences between the UK, Australian, and Canadian economic models. The request by the Formulary Working Group (FWG) was to assess denosumab for reducing the risk of developing skeletal-related events (SREs) in patients with bone metastases from breast cancer, non–small cell lung cancer (NSCLC), and OST.

Given the parameters of the information supplied and review, CADTH Common Drug Review (CDR) undertook a review of the cost-utility analysis report and Markov model comparing denosumab (Xgeva) primarily with zoledronic acid for advanced breast cancer patients with bone metastases over a lifetime time horizon from the Quebec societal perspective. Due to the short cycle length, a half-cycle correction was not implemented in the analysis. This analysis also included a scenario analysis comparing denosumab with pamidronate for the same indication, as well as information from the payer perspective. Cycle time was four weeks.

The manufacturer also provided reports on its economic submissions to PBAC and NICE, which presented information for the NSCLC and OST populations, but no models were submitted with these data. This and other publicly available information will be reviewed in a separate report by CDR.

The economic model provided by the manufacturer was a Markov model. Patients enter the model at age 57 years, and transition through three health states in the model: "on treatment", "off treatment", and "dead". The risk of an SRE was included for patients on and off treatment (Figure 1).

FIGURE 1: MODEL STRUCTURE PROVIDED BY THE MANUFACTURER



AE = adverse event; SRE = skeletal-related event.
Source: Manufacturer's submission to INESSS.[7]

The model was based on the SRE risk of all SREs pooled together including pathologic fractures, radiation to the bone, surgery to the bone, and spinal cord compression for each treatment.[7]

Treatment-emergent adverse events (AEs) were included in the "on treatment" health state. Patients cycled through health states every four weeks. Transition probabilities for treatment discontinuation and incidence of AEs were obtained from a head-to-head clinical trial in advanced breast cancer patients with bone metastases (Breast Cancer Study 136).[6] Efficacy data for denosumab versus zoledronic acid were obtained from Breast Cancer Study 136,[6] while information for pamidronate was informed from a mixed treatment comparison.[15] To evaluate efficacy in the primary comparison, the model used a fixed (constant) SRE rate over the lifetime of the model. The fixed SRE rate per patient per year was based on the rate of first and subsequent SREs, at least 21 days apart, in Breast Cancer Study 136 (0.3503 denosumab versus 0.4494 zoledronic acid), calculated by the number of events divided by the number of person-years in the study. All annual per-patient SRE rates were converted to four-week probabilities by dividing by 13 (to account for the number of four-week cycles in each year) and then converting to four-week probabilities, assuming an exponential relationship between rates and probabilities. The resulting four-week SRE probabilities were 0.0266 for denosumab and 0.0340 for zoledronic acid. Data for the "off treatment" health state were derived from a clinical trial investigating the efficacy of zoledronic acid compared with placebo, indicating the relative rate of at least one SRE was approximately 0.59 for zoledronic acid compared with the placebo group.[22] Patients from all treatment groups had an equal risk of death from any of the health states. Utility data and utility decrements associated with SREs were obtained directly from Breast Cancer Study 136.

Resource use associated with the treatment of SREs was determined through a Canadian retrospective chart review of 172 oncology patients with an SRE, which was supplied as an appendix to the submitted report.[7] Drug administration resource use and AE costs were based on the published literature, Régie de l'assurance maladie du Québec (RAMQ), the Ontario Case Costing Initiative, and input from a physician panel. The costs of zoledronic acid ($538.45) and pamidronate ($260.33) were derived from RAMQ (the denosumab drug acquisition cost — administered every four weeks — was based on price parity with the acquisition cost of zoledronic acid, also administered every four weeks). Generic zoledronic acid was not available at the time of analysis. Societal costs included lost productivity costs for the patient and caregiver related to SREs and drug administration and patient out-of-pocket parking costs related to drug administration visits. The resource use estimates were multiplied by the unit cost of the required resource to calculate the resource costs. Costs were reported in 2011 Canadian dollars.

The original model was validated by an independent group, and a technical validation on the adapted Canadian model was also conducted. The manufacturer reported the model results were validated, as the SREs predicted from the model showed very good agreement between the model and the actual observed events from the trial. The cumulative SRE rate for the trial (Breast Cancer Study 136) showed a linear increase in mean SREs per patient to justify that a fixed rate assumption was a reasonable approximation to the trial data. The manufacturer reported that in all cases, the lack of substantial and consistent curvature indicated a reasonably constant rate of events over time.[7]

One-way sensitivity analyses were conducted for all parameters as described in the base-case scenario. The sensitivity analyses were conducted by changing the relative parameter and re-running the probabilistic analysis for 2,000 iterations for the denosumab and pamidronate comparisons.

TABLE 6: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy: SRE rate (initial/subsequent)	Model used patient-level data derived from Breast Cancer Study 136 (ITT population; mean of 16 months on study for both ZA and denosumab), with a fixed, constant SRE rate over lifetime of the model. Annual per-patient SRE rates were converted to 4-wk probabilities by dividing by 13 (52 wks), assuming exponential relationship between rates and probabilities. SRE RR between denosumab and ZA based on fixed rate approach (0.78) was similar to the SRE RR derived from trial publication KM approach (0.77, *P* = 0.001).[6] Secondary analysis against pamidronate used data from an ITC for the pamidronate group and data from the head-to-head trial (Breast Cancer Study 136) for the denosumab group.	Although it would have been appropriate to use the data from Breast Cancer Study 136 when considering only denosumab vs. ZA, as a comparison against pamidronate was (appropriately) included, it is not appropriate to compare data from 2 different sources without these having been tested for consistency.
Natural history	After discontinuation of ZA or denosumab ("off treatment"), SRE risk based on the SRE rate for placebo patients who discontinued therapy (no therapy) in a trial comparing ZA with placebo for bone mets from breast cancer.	May not be appropriate. No analysis was presented to assess the comparability of the baseline characteristics between the ZA trial and Breast Cancer Study 136.
Utilities	SRE-associated utility values available from three sources: Breast Cancer Study 136 EQ-5D descriptive analysis; Breast Cancer Study 136 EQ-5D regression analysis; and a Canadian TTO study (Matza et al.).[a,23] In the base-case analysis, the EQ-5D descriptive analysis was used to model the impact of disease on utilities. The disutility values for the SREs were aggregated in the model to a single weighted value. The model indicated that when the values for Matza were used and weighted, the single disutility value was the same (0.063).	The report provides little justification for using the descriptive analysis; though the appendices indicate little difference between it and regression analysis values. The data from Matza et al. may have been appropriate to use given that the TTO exercise was undertaken in the general population of participants from the UK and Canada, though only ~30% of responders were Canadian. Although the provided model indicates that the single weighted disutility value was the same for Matza as the base-case value, the individual SRE values reported by Matza differ substantially.
Resource Use		
Drug administration	Based on product monographs.	Appropriate.
Discontinuation rate	Breast Cancer Study 136; number of discontinuations due to any reason other than death divided by the person-years of follow-up. Resulting annual discontinuation rate was converted to a 4-week probability.	The CDR Clinical Report indicated that one limitation of Breast Cancer Study 136 was that a high proportion of patients in both treatment groups (55%) discontinued from the study, mostly due to death and disease progression.
Lab monitoring	Based on expert opinion, patients are routinely monitored for renal function. This was not expected to change based on denosumab use, expected to be same as ZA, therefore not included in analysis.	Appropriate.
Adverse Events (Rates calculated by number of patients with each AE divided by time on study.[6])		

Data Input	Description of Data Source	Comment
Hypocalcemia	Breast Cancer Study 136; only patients receiving IV calcium were included in the analysis, to reflect patients with expected treatment cost.	Patients supposed to be taking suppl. calcium in addition to study meds, thus some uncertainty regarding adherence, and the generalizability of these rates to general practice.
ONJ	Breast Cancer Study 136; all grades of events were included.	Grading appropriate as treatment differs based on severity of ONJ and overall disease severity.
Renal toxicity	Breast Cancer Study 136; only grade 3/4/5 were included in the analysis as these were assumed to potentially lead to a hospitalization for treatment.	Appropriate.
Mortality	Overall mortality rates estimated by pooling mortality rates across treatment groups in Breast Cancer Study 136. Generalized gamma distribution reported as used to model OS based on comprehensive evaluation of possible parametric functions and reported best fit.	Appropriate.
Costs		
Drug	Zoledronic acid: RAMQ Denosumab: Amgen Canada Inc.	Appropriate in the context, but CDR reviewers have used costs from drug plans participating in CDR program; ODBF for denosumab and AB for ZA and pamidronate.
Administration (infusion cost)	Dranitsaris et al. 2001 (based on data from US Time and Motion study to which Canadian [Ontario] costs were applied) and RAMQ (2011).[9]	May overestimate infusion costs for pamidronate given infusion time longer than that stated in PM. Data based on observation of 6 patients.
Supplies	Dranitsaris et al. 2001 (based on data from US Time and Motion study to which Canadian [Quebec] costs were applied).	
Physician visit	RAMQ (2011).[9]	Appropriate in the context, but CDR reviewers have used costs from drug plans participating in the CDR program (Ontario Schedule of Fees).
Event: Pathologic fracture (symptomatic)	Canadian SRE costing study (Protocol ORS08-0106) 2011.	Some uncertainty with classification of patients between the costing study and the clinical study (Breast Cancer Study 136). CDR clinical expert indicated treatment of pathologic fracture was impacted by patient's severity of disease. Costs were not presented by cancer type, thus resource utilization associated with SREs for a breast cancer patient is uncertain.
Event: Radiation to the bone	Canadian SRE costing study (Protocol ORS08-0106) 2011.	Some uncertainty with classification of patients between the costing study and the clinical study (Breast Cancer Study 136). CDR clinical expert indicated in practice only patients with higher pain scores would receive radiation to the bone given the marginal benefits compared with the associated side effects. As the breakdown of events by pain score was not provided, uncertain whether the number of events is overestimated in both groups. The costs were not presented by cancer type, thus the resource utilization associated with SREs for a patient with breast cancer is uncertain.

Data Input	Description of Data Source	Comment
Event: Surgery to the bone	Canadian SRE costing study (Protocol ORS08-0106) 2011.	Some uncertainty with classification of patients between costing study and the clinical study (Breast Cancer Study 136). Costs were not presented by cancer type, thus resource utilization associated with SREs in breast cancer is uncertain.
Event: Spinal cord compression	Canadian SRE costing study (Protocol ORS08-0106) 2011.	Some uncertainty with classification of patients between costing study and the clinical study (Breast Cancer Study 136). CDR clinical expert indicated number of events small in Canadian clinical practice. Costs were not presented by cancer type, thus resource utilization associated with SREs for breast cancer is uncertain.
AEs (Hypocalcemia, hospitalized)	OCCI 2009/2010 (no indication of the codes used was provided).	While use of the OCCI was appropriate at the time, CDR is no longer able to test values from the OCCI. However, CDR would have been unable to do so as the manufacturer did not indicate which codes were used, thus the values used are associated with some uncertainty.
AEs (Grade 1 or 2 ONJ)	OCCI 2009/2010 (no indication of the codes used was provided).	
AEs (Grade 3, 4, or 5 ONJ)	OCCI 2009/2010 (no indication of the codes used was provided).	
AEs (Grade 3, 4, or 5 renal toxicity)	OCCI 2009/2010 (no indication of the codes used was provided).	

AB = Alberta; AE = adverse event; CDR = CADTH Common Drug Review; EQ-5D = EuroQoL 5-Dimensions Questionnaire; ITC = indirect treatment comparison; ITT = intention-to-treat; IV = intravenous; KM = Kaplan–Meier; mets = metastases; OCCI = Ontario Case Costing Initiative; ODBF = Ontario Drug Benefit Formulary; ONJ = osteonecrosis of the jaw; OS = overall survival; PM = product monograph; RAMQ = Régie de l'assurance maladie du Québec; RR = rate ratio; SRE = skeletal-related event; TTO = time trade-off; vs. = versus; wk = week; ZA = zoledronic acid.

[a] This document as originally referenced (Matza L, Van Brunt K, Baker T. Patient-reported utilities associated with skeletal-related events. 2010 Dec 6. Report No.: A2-8056) is not publically available; however, there has been a subsequent publication that appears to include the data.

TABLE 7: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The submitted model was tailored to the Quebec formulary review process.	While appropriate for the submission to INESSS, this is not appropriate for the submission to CDR. CDR PE reviewer's revised inputs in the model to be applicable to jurisdictions participating in the CDR program.
The appropriate comparator is ZA.	Formulary listings and PharmaStat data indicate that pamidronate and clodronate are also used in several provinces across Canada and may be more appropriate comparators in some provinces.
The primary comparator was ZA based on head-to-head study, while a secondary analysis versus pamidronate used data from an NMA for the pamidronate group only, allowing assessment of the 3 treatments together.	This is not appropriate as pamidronate data from the NMA is being compared with denosumab data from the head-to-head study (Breast Cancer Study 136). CDR clinical reviewers also found a high degree of uncertainty associated with the submitted NMA, thus the comparative efficacy is associated with uncertainty.
Use of a lifetime horizon is appropriate.	This is appropriate based on CADTH Economic Evaluation guidelines,[24] however, the CDR clinical expert indicated that the expected lifetime horizon for this patient group was likely to be substantially shorter than the 15 years modelled.

Assumption	Comment
SRE disutilities and costs can be aggregated to a single value.	May not be appropriate given the wide variation in disutility values and costs for each SRE. There is also uncertainty as to how events were coded to avoid the potential for double-counting (e.g., pathologic fracture leading to radiation to the bone, surgery), which would lead to double-counting of costs and disutilities.
Use of a constant rate for SREs.	As the data are from a short-term trial, it may underestimate the probability of future events.
Half-cycle correction not required given short cycle length.	Appropriate.
Use of KM estimates were appropriate.	Likely appropriate given the inclusion of censored data.
Comparability of population in costing study versus pivotal study (Breast Cancer Study 136).	No verification process appears to have been undertaken.
Costs from the Canadian costing study conducted in 2010/11 were appropriate to assess the health state costs.	The Costing Study took place at 2 sites, 1 in Quebec and 1 in Ontario. The Quebec site is unlikely to provide representative data for jurisdictions participating in the CDR program. CDR clinical expert indicated that although practice may not have changed in the past 5 years, the patient profile has changed, which may impact the costs. The SRE costs were based on 172 patients with varying cancer types. The results were not broken down by cancer type, thus the appropriate resource utilization associated with SREs for a patient with breast cancer is uncertain.

CDR = CADTH Common Drug Review; INESSS = l'Institut national d'excellence en santé et en services sociaux; KM = Kaplan–Meier; NMA = network meta-analysis; PE = pharmacoeconomic; SRE = skeletal-related event; ZA = zoledronic acid.

Manufacturer's Results from INESSS Submission

The model provided by the manufacturer reported that based on the probabilistic analysis with 2,000 iterations, denosumab had an extra 0.0111 QALYs per patient compared with zoledronic acid, fewer (undiscounted) SREs per patient, and overall lower cost (–$4,921). Thus, denosumab dominated zoledronic acid (Table 8). A supplemental scenario analysis in which pamidronate is considered as a comparator found denosumab also dominated pamidronate (Table 9). In both analyses, the results indicated slight incremental drug costs associated with denosumab due to discontinuation rates, but substantial costs savings based on treatment of AEs, administration costs, and SRE events.

TABLE 8: RESULTS OF THE MANUFACTURER'S BASE CASE (DENOSUMAB VERSUS ZOLEDRONIC ACID)

Results	Denosumab	Zoledronic Acid	Difference (Denosumab – Zoledronic Acid)
Sum drug and administration costs	$12,997	$17,020	–$4,023
SRE and AE costs	$6,841	$7,737	–$896
Total costs	$19,837	$24,758	–$4,921
QALY	2.0408	2.0297	0.0111
Cost per QALY	NA	NA	Dominant

AE = adverse event; NA = not applicable; QALY = quality-adjusted life-year; SRE = skeletal-related event.
Source: Adapted from manufacturer's submission to INESSS.[7]

TABLE 9: RESULTS OF THE MANUFACTURER'S SCENARIO CASE (DENOSUMAB VERSUS PAMIDRONATE)

Results	Denosumab	Pamidronate	Difference (Denosumab – Pamidronate)
Sum drug and administration costs	$12,997	$11,668	$1,329
SRE and AE costs	$6,841	$8,536	–$1,695
Total costs	$19,837	$20,204	–$367
QALY	2.0408	2.0163	0.0245
Cost per QALY	NA	NA	Dominant

AE = adverse event; NA = not applicable; QALY = quality-adjusted life-year; SRE = skeletal-related event.
Source: Adapted from manufacturer's submission to INESSS.[7]

The manufacturer undertook a series of one-way sensitivity analyses based on the probabilistic model. Using alternate clinical, cost, and utility inputs, the manufacturer reported that denosumab maintained dominance over zoledronic acid in each of these deterministic sensitivity analyses. The manufacturer ran the same sensitivity analyses for the scenario analysis comparing denosumab with pamidronate, and reported denosumab dominated pamidronate in all but one analysis (cost of pamidronate administration at 50% of base case).

APPENDIX 4: REVIEW OF THE PUBLISHED LITERATURE

As no formal submission was presented to the CADTH Common Drug Review (CDR), CDR undertook a review of the published economic studies of denosumab for patients with bone metastases secondary to breast cancer to provide supportive information.

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 and daily updates via Ovid; Embase (1974–) via 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 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 literature search was conducted by an information specialist and identified 150 economic abstracts, of which nine received full text review (Ford et al. [2013],[15] Yfantopoulos et al. [2013],[12] Stopeck et al. [2012],[10] Lothgren et al. [2013],[11] Carter et al. [2013],[25] Carter et al. [2012],[26] Xie et al. [2012],[14] Snedecor et al. [2012],[13] and Koo et al. [2013][27]) 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,[25] did not present results for the breast cancer indication,[26] or were reviews of studies that were already captured in the literature search[27] were not included in the literature review. The literature search identified six economic evaluations of denosumab for patients with bone metastases secondary to other solid tumours (not including prostate or breast cancers). None of six studies economic evaluations identified were undertaken in the Canadian health care setting. Five of the six studies were industry-sponsored — two by Amgen (Stopeck et al.[10] and Lothgren et al.[11]) and three

by Novartis (Yfantopoulos et al.,[12] Snedecor et al.,[13] and Xie et al.[14]) — and one was a study by an independent review group in the UK (Ford et al.[15]).

In all of the studies, the primary comparator for denosumab was zoledronic acid. One study (Lothgren et al.[11]) was a European budget impact assessment based on a patient switching from zoledronic acid to denosumab, while the other five 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 incremental cost-effectiveness ratios (ICERs) ranged from denosumab being dominant where a patient access scheme was in place (essentially a reduced price)[15] to €380,000 per quality-adjusted life-year (QALY) (exchange rate 2012 € to 2012 C$: €1 = C$1.2850)[16] for denosumab compared with zoledronic acid.[12] Without a patient access scheme in place, the ICER was assessed to be greater than £200,000 per QALY[15] (exchange rate 2010 £ to 2012 C$: £1 = C$1.5918).[16] Common to each of these studies, at a willingness-to-pay (WTP) threshold of $50,000 per QALY or per skeletal-related event (SRE) avoided, denosumab was not cost-effective. These findings are aligned with the results obtained from the manufacturer's economic model.

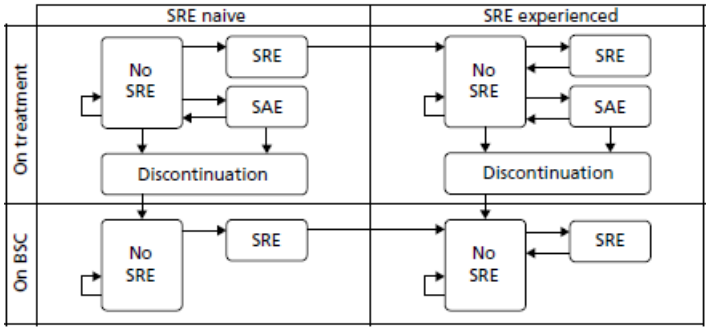
These articles are summarized individually below.

Summary of Individual Studies

Ford et al. (2013; Independent)

Ford et al.[15] undertook a health technology assessment 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 a manufacturer-submitted economic model. The submitted model was 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 own economic analysis. The model divided patients into SRE naive at start of treatment, and patients who were SRE experienced at the start of treatment. When patients were on treatment, they could have an SRE, adverse event, or discontinue. Patients could also transition to BSC. The model was similar to that submitted to CDR.

FIGURE 2: MODEL STRUCTURE FROM FORD ET AL.



BSC = best supportive care; SAE = serious adverse event; SRE = skeletal-related event.
Source: Reproduced with permission from Ford J, Cummins E, Sharma P, Elders A, Stewart F, Johnston R, Royle P, Jones R, Mulatero C, Todd R, Mowatt G. Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. Health Technol Assess. 2013 Jul;17(29):1-386.[15]

The primary assumption of the model was 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 four studies for breast cancer patients suitable for the NMA. The results of the NMA found that denosumab was effective in delaying time to first SRE and reducing the risk of multiple SREs compared with zoledronic acid; was similar to zoledronic acid for quality of life, pain, overall survival, and safety; and that while denosumab appeared more effective in delaying SREs than placebo, this was limited by numerous areas of uncertainty. The clinical information in the Ford et al. model appears to have been at least similar to the information presented in the model provided by the manufacturer.

Cost parameters used in the model appear to be the same as those in the model provided to CDR; however, the cost inputs for the Ford et al. model were informed from British National Formulary prices, and a survey of oncology nurses and pharmacists who indicated that denosumab would result in staff time savings compared with zoledronic acid per administration. Total annual drug costs indicated that without the patient access scheme (PAS), denosumab was the most expensive, followed by pamidronate, then ibandronic acid, and zoledronic acid being the cheapest option. Costs are in 2010 £ (exchange rate 2010 £ to 2010 C$: £1 = C$1.5918).[16]

Cost-utility modelling results for denosumab relative to zoledronic acid were driven by the availability of a PAS for denosumab. Ford et al. reported the manufacturer's analysis indicated that without the PAS, denosumab was not estimated to be cost-effective compared with zoledronic acid, reporting an ICER above £100,000 per QALY for the SRE-experienced other solid tumours (OST) patient population (SRE-naive was compared with BSC only). For the breast cancer population, the additional patient benefit of denosumab over zoledronic acid was small: 0.007 QALYs. With the PAS, denosumab dominated zoledronic acid.

The authors undertook substantially more reanalyses than were presented by the manufacturer (including subgroup analyses), finding that for breast cancer — without the PAS — the ICER for denosumab versus zoledronic acid ranged between £190,000 and £380,000 per QALY, depending upon whether the SREs were assessed on average or individually (0.003 QALYs for average, 0.006 QALYs for individual). With the PAS, the ICER improves to dominating zoledronic acid, or having an ICER of £3,800 per QALY. The authors presented analyses comparing denosumab with BSC and other bisphosphonates;

the probabilistic analyses indicated a 98% likelihood of denosumab being cost-effective compared with bisphosphonates at a WTP threshold of £20,000 per QALY, and 100% likelihood at a WTP threshold of £30,000 per QALY. In patients contraindicated to bisphosphonates, the probabilistic analyses reported a gain of 0.028 QALYs and estimated ICER of £154,944 per QALY, and a 0% likelihood of denosumab being cost-effective compared with BSC at a WTP threshold 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 had some uncertainty around the suitability of the utility values applied, the NMA was subject to numerous uncertainties, and given the small patient gains estimated (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 were concerned with BSC being assumed to have a zero incidence of the modelled serious adverse events (SAEs), as without treatments to curb SREs, possible SAEs come to the fore. Although there may be some potential for differences in pricing and dosing between the UK and Canadian settings, 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. (2012; Amgen-Sponsored)

Stopeck et al.[10] 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 non–small cell lung cancer (NSCLC). The model was structured identically for both treatments and across all tumour types, but with treatment and tumour-specific model inputs. Similar to the model provided to CDR, the model by Stopeck et al. consisted of three Markov health states: "on treatment", "off treatment", and "dead". Treatment discontinuation was also incorporated into the model. While on treatment, patients experienced an SRE risk, adverse event (AE) risk, disutility, and various costs associated with SREs, AEs, and treatment; while off treatment, patients experienced an SRE risk, which is associated with a disutility and a cost. Clinical data were derived primarily from the results of three pivotal head-to-head phase 3 clinical trials comparing denosumab with zoledronic acid every four weeks, though real-world SRE rates for zoledronic acid–treated patients were incorporated from a large commercial database. Patients cycled through these health states every 28 days, with constant rates used over the lifetime of the patient. 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. The majority of these parameters match the model provided to CDR (though fewer patients had transitioned to the "dead" state in the model provided to CDR).

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. All treatment costs were sourced from US sources (nationally representative commercial claims database and privately held wholesalers). Costs and QALYs were discounted at 3% annually. One-way and probabilistic sensitivity analyses were conducted. The cost profiles appear to have differed from the model inputs provided to CDR.

Stopeck et al. found denosumab was associated with a reduction in the number of SREs compared with zoledronic acid as well as an increase in patients' quality of life in all populations; accruing an incremental 0.17 QALYs at a cost of $13,451, resulting in an ICER of $78,915 per QALY compared with zoledronic acid for the breast cancer population. The results were sensitive to drug costs, discontinuation, and SRE rates. The probabilistic sensitivity analysis found the probability of denosumab being cost-effective at a WTP threshold of $100,000 per QALY to be 62%. The total incremental QALYs were higher than any other published values, and substantially higher than the incremental QALYs in the model provided to CDR.

Lothgren et al. (2013; Amgen-Sponsored)

Lothgren et al.[11] 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 over a one-year time horizon. Thus, as a budget impact assessment, the results differ substantially from the economic model reviewed by CDR. Country-specific medication, administration, and patient management costs were included. SRE-related costs were obtained from a retrospective chart review of bone metastases secondary to various cancer types in patients across Europe (Austria and Sweden), or in-patient and outpatient data (Switzerland). Frequency of zoledronic acid administration was informed by real-world data. SRE rates were sourced from direct head-to-head trials of denosumab and zoledronic acid. The authors presented the results stratified by breast cancer, prostate cancer, and OST. Costs were converted to 2012 euros.

The authors reported that transitioning from zoledronic acid to denosumab was associated with cost savings in all countries, which for breast cancer specifically ranged between €1,853 (Austria) to €3,562 (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 to 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. (2013; Novartis-Sponsored)

Yfantopoulos et al.[12] 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 reported that they adapted an excel-based model developed by Lothgren et al. for the same population in the Dutch setting, and stratified the population to three cancer types: breast cancer, prostate cancer,

and OST. 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. Only direct medical costs were included (i.e., drug acquisition, administration, SREs, and patient monitoring). The analyses for the three cancer types were conducted 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 clinical information was sourced from phase 3 RCTs, while 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 presented 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 (0.012 to 0.0125; 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 (exchange rate 2012 € to 2012 C$: €1 = C$1.2850)[16] for breast cancer, €61,296 for prostate cancer, and €80,830 for OST. In scenarios 2 and 3, results indicated that the incremental cost per QALY was above €100,000 per QALY for all indications (scenario 2 range: €112,414 to €163,993; scenario 3 range: €198,431 to €328,364), with the ICER for breast cancer falling in the middle in both scenarios.

Thus, 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 in the Greek setting. These findings, while similar to the economic evaluation provided to CDR, may not be transferrable to the Canadian setting due to the potential differences in setting as noted by Yfantopoulos et al.

Snedecor et al. (2012; Novartis-Sponsored)

Snedecor et al.[13] undertook a study to determine the cost-effectiveness of denosumab versus zoledronic acid for patients with bone metastases secondary to breast cancer from a US payer perspective.

The authors developed a literature-based Markov model to estimate the SRE incidence, survival, QALYs, drug-related costs, and cost of SREs in patients receiving denosumab versus zoledronic acid. The base-case analysis was conducted over a 27-month time horizon, while a 60-month scenario analysis was also undertaken. The model incorporated monthly cycles of patient progression through seven mutually exclusive health states prior to death (eight health states in all). The model did not explicitly consider AEs or disease progression as the data indicated no significant differences between treatments for these parameters. Transition probabilities were based on published literature (Stopeck et al.) and Weibull models were used to approximate the curves. The authors undertook a literature search to identify a baseline utility value and utility decrements. Where utility values for the various health states were based off an initial value of 1, the authors multiplied the health state utility by the baseline utility value. The authors also indicate they took into account the length of the impact on quality of life when assessing events that impacted utility values. Discontinuation was based on rates reported in the article by Stopeck et al. All model costs were based on US sources and inflated to 2010, with costs discounted

at 3% per annum. This model differed substantially from the one provided to CDR, given the number of health states, exclusion of AEs, impact duration for events, and discount rate.
The results of the model found patients receiving denosumab had fewer SREs and accrued more QALYs than patients receiving zoledronic acid (0.0102), but had higher treatment costs ($7,107), resulting in an incremental cost per QALY of $697,499 (exchange rate 2010 US$ to 2010 C$: US$1 = C$1.0299)[16] compared with zoledronic acid. Deterministic and probabilistic sensitivity analyses indicated the ICER was below $100,000 per QALY in less than 1% of iterations.

Snedecor et al. compared and contrasted the results of their economic evaluation to the findings of other published studies, finding that most other studies were undertaken over a longer time horizon and reported greater benefit for denosumab. However, the authors argue that their analysis was not biased against denosumab and that the findings of their study should not be interpreted that denosumab is not effective, but as a guide to determine the economic value of denosumab and zoledronic acid. Although the model structure and costs used differed, the model results suggest that although denosumab is associated with marginally higher QALYs, it is also associated with higher costs.

Xie et al. (2012; Novartis-Sponsored)
Xie et al.[14] undertook a study to assess the cost-effectiveness of denosumab versus zoledronic acid in the prevention of SREs in patients with advanced breast cancer and bone metastases in the US from a third-party payer perspective.

The authors developed a Markov model to compare the costs and effectiveness of denosumab versus zoledronic acid in the prevention of SREs and pathologic fractures in patients with advanced breast cancer with bone metastases over a one-year time horizon, using four-week cycles. The short time horizon was justified given the preferences of US payers, and impending availability of generic zoledronic acid. The model includes direct costs (i.e., drug treatment costs, non-drug costs) and effectiveness outcomes (i.e., number of SREs and pathologic fractures). A hypothetical cohort of patients transitioned through the 11 health states of the Markov model based on a combination of SRE status (no SRE, experiencing a first on-study SRE, experiencing a subsequent SRE, no SRE but having a history of SRE) and SRE type (pathologic fracture, radiation to the bone, surgery to the bone, spinal cord compression), receiving either denosumab or zoledronic acid. All patients started with no SRE and no history of SRE. The transition probabilities were estimated using the publicly available clinical trial data. The majority of costs were based on direct US sources (e.g., fee schedules) or published literature, and updated to 2011 US$ where required. The authors undertook deterministic and probabilistic sensitivity analyses to assess variations in key model inputs. The primary outcome of the study was a cost per SRE avoided; cost per pathologic fracture was a secondary outcome. The model appears to differ to the one provided to CDR based on the structure (health states, time horizon) and cost data.

The results of the model found that over one year, patients receiving denosumab had fewer SREs (0.06) than patients receiving zoledronic acid, but had higher treatment costs ($6,522), resulting in an incremental cost of $114,628 (exchange rate 2011 US$ to 2011 C$: US$1 = C$0.9891)[16] per SRE avoided compared with zoledronic acid. The cost per pathologic fracture avoided was higher ($290,136). Univariate and probabilistic sensitivity analyses were conducted to test the sensitivity of the model, with the univariate sensitivity analyses indicating an ICER ranging from $17,000 per QALY to zoledronic acid dominating denosumab. The probabilistic sensitivity analysis indicated that denosumab at WTP thresholds of $100,000, $50,000, and $30,000 per SRE avoided, denosumab was cost-effective compared with zoledronic acid in 44%, 30%, and 17% of iterations at the end of one year.

Although the models appeared to differ, Xie et al. noted several limitations similar to those identified by CDR. Data from various different sources were used to identify cost and effectiveness inputs, thus inconsistencies between study populations, approaches, and databases could lead to potential bias in the study results; International Classification of Diseases (ICD) codes used to identify SREs in the denosumab study were not able to be verified against a clinical dataset, thus the extent to which those costs actually represent the costs associated with the SREs measured in the trial are uncertain; costs for SRE events from the literature might not be directly applicable to the population or setting, and assumptions around SRE distribution have been made.

APPENDIX 5: PRICE REDUCTION SCENARIO WHERE PROVINCE FUNDS INFUSIONS

CADTH Common Drug Review (CDR) undertook a price reduction analysis on the sensitivity analysis assuming that the province is required to fund infusion costs (based on the costs presented by Dranitsaris et al.).[28]

TABLE 10: CADTH COMMON DRUG REVIEW PRICE REDUCTION SCENARIOS BASED ON PROVINCE FUNDING INFUSIONS

ICURs for Denosumab Based on Infusion Funded by Plans			
Price of Denosumab	**Manufacturer Denosumab Versus ZA and Pamidronate[a]**	**CDR Analysis**	
		Denosumab Versus Generic ZA	**Denosumab Versus Generic Pamidronate**
Ontario ($575.55)	Dominant[a]	$376,094/QALY	$197,475/QALY
10% reduction ($518.00)	Dominant	$265,212/QALY	$141,249/QALY
15% reduction ($489.22)		$202,332/QALY	$113,136/QALY
20% reduction ($460.44)		$139,452/QALY	$85,024/QALY
25% reduction ($431.66)		$76,572/QALY	$56,911/QALY
30% reduction ($402.89)		$13,692/QALY	$28,798/QALY
35% reduction ($374.11)		Dominant	$685/QALY
40% reduction ($345.33)			Dominant

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; ZA = zoledronic acid.

[a] Manufacturer's base-case analysis is dominant using the submitted INESSS price and the listed Ontario price.

APPENDIX 6: OTHER POTENTIAL COMPARATOR TREATMENTS

TABLE 11: OTHER POTENTIAL TREATMENTS FOR BONE METASTASES IN PATIENTS WITH BREAST CANCER

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 (generic)	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 tab etidronate for 14 days, then 1 tab 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 October 2015) prices unless otherwise stated.

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