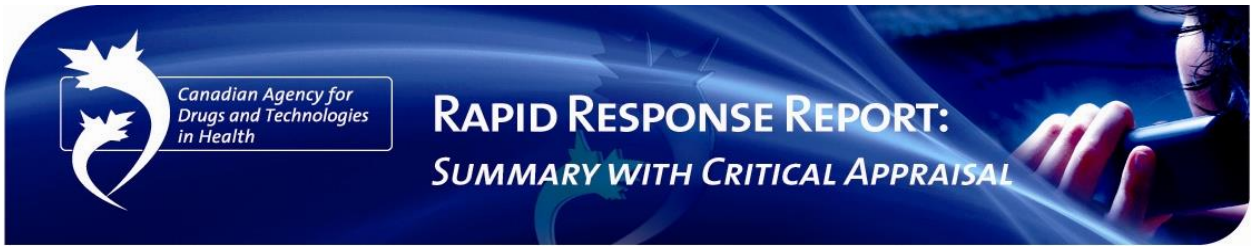

TITLE: Denosumab versus Zoledronic Acid for Adults with Osteoporosis: A Review of Cost-Effectiveness

DATE: 12 December 2016

CONTEXT AND POLICY ISSUES

Osteoporosis is a progressive disease characterized by a reduction in bone mineral density (BMD), which leads to weakening of the bones and increased risk of fracture.[1] It is a common condition, affecting up to 10.5% of Canadians over the age of 50[2] with an associated economic burden of osteoporosis-related fractures reported at $4.6 billion.[3] Treatment for osteoporosis and measures for fracture prevention in men and women are generally similar, and can include diet, exercise, and lifestyle changes (e.g., stopping smoking and reducing alcohol intake).[4,5] Oral bisphosphonates (e.g., alendronate, risedronate) are the typical first-line pharmacological interventions indicated for use in patients with osteoporosis to increase BMD; however, alternative non-oral drug options can be offered to patients who cannot tolerate oral administration or for whom adherence is a concern.[6,7]

Zoledronic acid is a bisphosphonate that is administered intravenously (IV) once yearly (marketed as Aclasta and also available as a generic). It is indicated for the treatment of postmenopausal women to reduce the incidence of fractures, and for the treatment of men with osteoporosis to increase BMD.[8] An alternative non-oral treatment option for osteoporosis is denosumab, which is a monoclonal antibody that is administered subcutaneously (SC) every six months (marketed as Prolia). Denosumab is indicated for the treatment of osteoporosis in men and women at high risk of fracture.[9] It is also indicated to increase BMD in certain subgroups of patients at high risk of fracture, including men receiving androgen deprivation therapy for non-metastatic prostate cancer, and women receiving adjuvant aromatase inhibitor therapy for non-metastatic breast cancer.[9]

The CADTH Common Drug Review (CDR) has reviewed denosumab for postmenopausal women and men with osteoporosis, and the Canadian Expert Drug Committee (CDEC) made listing recommendations based on those reviews.[10,11] CDEC noted that zoledronic acid is the most relevant comparator for denosumab, and that denosumab is more costly than generic zoledronic acid and comparable in price to branded zoledronic acid.[10,11] The CDR recommendations also discussed indirect evidence that suggests there is no statistically

significant difference between zoledronic acid and denosumab for treating postmenopausal women with osteoporosis who are at risk for fracture, but given a high degree of uncertainty regarding the true relative effectiveness of denosumab compared with zoledronic acid, CDEC recommended listing denosumab for the treatment of osteoporosis in women at a reduced price.[10] The CDR review and CDEC deliberations were limited to cost-comparisons and other cost information that was available in the public domain.[11] An updated review of the available cost-effectiveness evidence for these two agents will help to determine if there is a more cost-effective non-oral agent for the treatment of male and female patients with osteoporosis, particularly given the availability of generic zoledronic acid at a lower cost than the branded options.

The purpose of this report is to evaluate the cost-effectiveness of denosumab and zoledronic acid for the treatment of postmenopausal women and men with osteoporosis, including women receiving adjuvant aromatase inhibitor therapy for non-metastatic breast cancer, men receiving androgen deprivation therapy for non-metastatic prostate cancer, and patients with severe renal dysfunction.

RESEARCH QUESTION

What is the cost-effectiveness of denosumab versus zoledronic acid in patients with osteoporosis?

KEY FINDINGS

Two studies were identified that evaluated the cost-effectiveness of denosumab for the treatment of elderly men with osteoporosis, from a payer perspective in the United States or Sweden. Both studies found that subcutaneous denosumab 60 mg administered once every six months was associated with lower-costs and higher health benefits than intravenous zoledronic acid administered once a year, even when the price of zoledronic acid was lowered to consider the impact of generic drug pricing. Therefore, the authors concluded that denosumab was a cost-effective option for the treatment of elderly men with osteoporosis in the United States and Sweden. However, treatment efficacy inputs for the model were derived from fracture risk data in women. This decision was based on the similar post-treatment bone mineral density changes in men and women but direct evidence of fracture risk reduction in men was not available; therefore, results should be interpreted with caution. Both included studies were authored by individuals affiliated with the manufacturer of subcutaneous denosumab 60 mg; the potential impact of industry involvement on the findings is unclear. No evidence regarding the cost-effectiveness of denosumab versus zoledronic acid was identified for alternative populations (e.g., postmenopausal women or patients with non-metastatic cancer) or in a Canadian setting.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and economic studies. Where possible, retrieval was limited

to the human population. The search was also limited to English language documents published between January 1, 2011 and November 14, 2016.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with osteoporosis *Subpopulations of interest* • *Postmenopausal women with osteoporosis* • *Women receiving adjuvant aromatase inhibitor therapy for non-metastatic breast cancer* • *Men with osteoporosis* • *Men receiving adjuvant anti-androgen treatment for non-metastatic prostate cancer* • *Patients with severe renal dysfunction*
Intervention	Denosumab (Prolia)
Comparator	Zoledronic acid (Aclasta)
Outcomes	Cost-effectiveness outcomes (e.g., cost per QALY or health outcome)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, economic evaluations

QALY = quality-adjusted life year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011.

Critical Appraisal of Individual Studies

The included economic studies were assessed using the Drummond checklist.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 146 citations were identified in the literature search. Following screening of titles and abstracts, 135 citations were excluded and 11 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the 11 potentially relevant articles, nine publications were excluded for various reasons, while two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study Design and Country of Origin

Two cost-effectiveness analyses (CEAs) were identified for this review.[13,14] Both studies were published by groups in the United States and were based on the same cohort Markov model with six month cycles over a lifetime horizon. The CEA by Silverman et al.[13] was conducted using an American payer perspective, and the CEA by Parthan et al.[14] used a Swedish payer perspective.

Patient Population

Both studies considered a patient population of elderly men (at least 75 years old) with osteoporosis.

Interventions and Comparators

SC denosumab 60 mg every six months was compared with alternative treatments for osteoporosis, including IV zoledronic acid 5 mg once yearly, oral bisphosphonates (alendronate, risedronate, ibandronate), and teriperatide.[13,14] Parthan et al.[14] additionally considered strontium ranelate as a comparator. Treatment duration was assumed to be up to five years for denosumab and zoledronic acid. Adherence to denosumab was estimated based on a study of patient adherence, preference, and satisfaction of denosumab in postmenopausal women with low BMD; adherence to zoledronic acid was assumed to be the same as that for denosumab. The duration of treatment effectiveness after completion of therapy, or "offset time", was assumed to be two years in the base case analysis.[13,14]

Outcomes

Costs and clinical outcomes over a lifetime horizon were modelled for each drug treatment. All outcomes were discounted at 3% annually.

Clinical outcomes included fracture risk (hip, vertebral, or other fractures), mortality, and quality of life. Model inputs related to treatment efficacy were derived from the published literature. In the absence of published evidence of fracture risk in men with osteoporosis, this risk was estimated from data in postmenopausal women. Both studies provided the rationale that BMD changes in response to treatment are similar in these two populations, which may reasonably translate to similar changes in risk of fracture. Risk of mortality after fracture was based on rates in a Swedish population for both studies, as these data for an American population were not available for Silverman et al.[13] Baseline age-specific utility weights used by Parthan et al.[14] were based on normal Swedish men using EuroQOL-5 Dimension (EQ-5D); the source of background utilities in Silverman et al.[13] was not reported. Both studies identified the post-fracture utility data from a meta-analysis and provided fracture site-specific utility multipliers. It was assumed that non-hip, non-vertebral (NHNV) fractures did not affect quality of life after the first year following the fracture.

Relevant costs included those associated with the drug intervention, drug administration and monitoring costs, costs associated with treating fractures, and long-term care costs for patients who suffered a hip fracture. All costs were provided in 2013 USD[13] or 2012 euros.[14] In both

CEAs, age-specific fracture costs by site were derived from studies with combined male and female study populations; however, Parthan et al.[14] identified published evidence for hip fracture costs in men. Long-term care costs for the model were estimated from data for women.

Both studies reported incremental cost-effectiveness ratios (ICERs; cost per life year saved and cost per quality-adjusted life year [QALY] gained) for the osteoporosis treatment options based on multi-way CEA.

Sensitivity Analyses

The authors performed sensitivity analyses adjusting the parameters by the published confidence intervals or standard errors; in the absence of these published data, parameters were varied by 25% above and below the base case value.[13,14] To estimate the impact of a lower drug acquisition cost of generic zoledronic acid on the results, this value was reduced by 35%[13] or 75%[14] from the base case cost in sensitivity analyses. The reason for the difference in price reduction between the two studies was unclear, though it may reflect different approaches to generic drug pricing in the United States versus Sweden. To compare with other models that use a five year offset time for bisphosphonates, sensitivity analyses were conducted in both studies that increased the offset time from two to five years for zoledronic acid; offset time for denosumab was held at two years to be conservative. Parthan et al.[14] also evaluated a fracture risk after treatment that remained constant with age, unlike the base case analysis that considered drug efficacy specifically in patients over the age of 75. Probabilistic sensitivity analyses were also run in both studies to assess uncertainty in the model.

Summary of Critical Appraisal

Overall, the study designs and data collection methods of both CEA were well reported, and the assumptions and interpretations of the findings were reasonable. The publications had clear research questions framed by their economic importance. The type of analysis performed, perspective, time horizon, interventions and comparators, resource use, and costs were also clearly reported and justified where necessary. Both publications used the same Markov model which had been previously designed and published for postmenopausal women with osteoporosis in the United States[15] and Sweden;[16] references to publications with more detailed methods were provided.

The published sources of effect estimates and utilities were provided; however, the details of the design and results of the effectiveness studies were not described in either publication,[13,14] and Silverman et al.[13] did not provide details of the studies from which the utilities were derived. It was also unclear in the study by Silverman et al.[13] whether long-term care stays after a hip fracture were assumed to be permanent in the model; however, this is likely to be the case as this assumption was described by Parthan et al.[14] Both groups estimated denosumab compliance rates based on the DAPS (Denosumab Adherence Preference Satisfaction) study of postmenopausal women,[17] which is a reasonable source if there are no expected differences between women and men in acceptance of a SC injection every six months. In addition, modelling by Silverman et al.[13] predicted that 73.6% of patients are compliant with denosumab at one year, which was reasonable when compared with compliance rates (ranging from 70% to 82%) observed in denosumab trials at similar time points. The model also assumed that adherence to all injectable comparators, including zoledronic acid, was the same as adherence to denosumab, which is likely reasonable given the similarly infrequent dosing regimens (once every six months for denosumab and once per year for zoledronic acid). The assumption of

similar treatment efficacy in men and postmenopausal women (similar post-treatment changes in fracture risk) was acceptable given the lack of direct evidence of fracture risk reduction in men. However, uncertainty was introduced to the model by extrapolating indirect evidence in men (post-treatment BMD changes) to fracture risk reduction based on similar post-treatment BMD changes in men and women.

Limitations in some model assumptions were reported by both groups. Due to the hierarchical structure of the Markov model, patients who experienced a fracture could not subsequently experience a milder fracture type (severity increases from NHNV fracture, to vertebral fracture, to hip fracture); therefore, the incidence of milder fractures was likely underestimated.[13,14] In addition, the published source of the estimate for the risk of NHNV fractures included hip-fractures; this may have overestimated the number of NHNV fractures.[13,14] Finally, both groups reported the assumption that there were no long-term costs (after one year post-fracture) for vertebral and NHNV fractures, which may have underestimated costs.[13,14] However, the related assumption that there was no long-term impact on quality of life in these situations that may be inappropriate given the advanced age of patients in the model and potential severity of some types of NHNV fractures, and may have underestimated associated disutilities. Both studies suggested that these overestimates and underestimates would be slight, though this suggestion was not justified.

The outcome measures explored for these CEAs were appropriate and clearly described. In both studies, the discount rate for outcomes was stated but not justified. Data were presented disaggregate form in both publications, including the quantity or frequency of resource use, unit costs and total cost. Both publications described adjusting costs for inflation. Both groups described sensitivity analyses with conservative variation around the base case value (25% above and below) in the absence of published data regarding a range of results. Both groups reported their findings in the recommended format of incremental analysis, in which treatment strategies are ranked in order of increasing cost, and ICERs were calculated in that order. The conclusions directly followed the results of this incremental analysis, and the parameters that affected the results upon variation in sensitivity analyses were also reported.

Summary of Findings

In multi-way cost-effectiveness analyses, Silverman et al.[13] found that generic alendronate was the least costly treatment option, followed by denosumab. For the comparison of denosumab against the generic alendronate reference, the incremental cost per life year saved was $26,389 and the incremental cost per QALY gained was $16,888. These ICERs were sensitive to changes in the relative risk of hip fracture with either drug, the cost of denosumab, and the cost of a day in a nursing home. Denosumab dominated zoledronic acid, risedronate, ibandronate, and teriparatide; that is, denosumab was associated with lower costs and higher health benefits (life years and QALYs) than all other comparators. These results were robust to a 35% reduction in the price of zoledronic acid and variation in offset times. Probabilistic sensitivity analyses showed an 85.8% probability of denosumab being cost-effective compared with other treatments at a threshold of $100,000/QALY.[13]

In multi-way cost-effectiveness analyses, Parthan et al.[14] found that denosumab was the least costly treatment option and dominated all other comparators, including zoledronic acid. Denosumab still dominated the comparators in sensitivity analyses where the price of zoledronic acid was reduced by 75%, offset times were varied, and alternative efficacy data inputs for

zoledronic acid were used. The authors did not present an ICER for the sensitivity analyses that assumed no change in fracture risk with age (using efficacy data from postmenopausal women), but reported that the incremental cost for patients on denosumab was €266 more than the cost of zoledronic acid with a difference of 0.004 QALYs. Probabilistic sensitivity analyses showed a 96.1% probability of denosumab being cost-effective compared with other treatments at a threshold of €66,000/QALY.[14]

The studies concluded that denosumab is a cost-effective option for the treatment of elderly men with osteoporosis, in either the United States[13] or Sweden.[14]

Limitations

The main limitations of this review are related to limited study populations and generalizability of findings. The included studies evaluated the cost-effectiveness of denosumab from a payer perspective in the United States[13] and Sweden;[14] it is unclear whether these results would be applicable in a Canadian health care setting. No studies were identified for inclusion that compared the cost-effectiveness of denosumab with zoledronic acid in women. Furthermore, both included studies[13,14] used the same Markov model with a target population reflective of one clinical trial population (men age 75 and older); this group may not be representative of all men with osteoporosis, including other patient subgroups of interest, such as men receiving androgen deprivation therapy for non-metastatic prostate cancer or women receiving aromatase inhibitor therapy for non-metastatic breast cancer. Another limitation of the model was that it did not consider pre-treated patients or sequential treatment, which may not be reflective of clinical practice. In the absence of efficacy data, post-treatment risks of fracture for the model were estimated from data in postmenopausal women. While this assumption may be reasonable due to similar BMD outcomes in men and women after drug therapy, direct evidence regarding this outcome in men is lacking and introduces some uncertainty about the study findings. Finally, the study by Silverman et al.[13] was funded by Amgen, the manufacturer of denosumab for the treatment of osteoporosis (Prolia), and all authors were either employees of Amgen or received consulting fees from this company; it is unclear whether this funding and employment relationship may have impacted the study conduct and findings. Although the source of funding and author conflicts of interest were not reported for the study by Parthan et al.,[14] there was complete overlap in the authors for the two studies.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In two cost-effectiveness analyses,[13,14] SC denosumab 60 mg administered once every six months was associated with lower-costs and higher health benefits than IV zoledronic acid administered once a year, even when the price of zoledronic acid was lowered to consider the impact of generic drug pricing. Therefore, the authors concluded that denosumab was a cost-effective option for the treatment of elderly men with osteoporosis in the United States[13] and Sweden.[14] They suggested that these results were driven by differences between drug treatments in fracture risk reduction and high compliance with denosumab, and that the economic benefits of denosumab are likely more apparent in this elderly population at higher risk for serious and costly hip fractures.[13,14] However, treatment efficacy inputs for the model were derived from fracture risk data in women based on the similar post-treatment BMD changes in men and women; therefore, results should be interpreted with caution. Both included studies were authored by individuals affiliated with the manufacturer of SC denosumab 60 mg, and the potential impact of industry involvement on the findings is unclear.

The CDEC recommendations for the use of denosumab in men with osteoporosis relied on clinical evidence from one randomized placebo-controlled trial that evaluated changes in BMD rather than fractures. For that CDR submission, the manufacturer also provided two network meta-analyses (NMAs) comparing denosumab with zoledronic acid. The results of the NMAs suggested similar post-treatment changes in BMD with denosumab and zoledronic acid; however, due to the small number of studies and between-study heterogeneity, CDEC considered the results of the NMAs to be uncertain.[11] As no direct evidence of the clinical effectiveness of denosumab for the reduction in fracture risk in men with osteoporosis was available for the CEAs summarized in this report, Silverman et al.[13] and Parthan et al.[14] made assumptions about the main clinical efficacy inputs that introduced uncertainty in the findings.

No evidence regarding the cost-effectiveness of denosumab versus zoledronic acid was identified for alternative populations (e.g., postmenopausal women or patients with non-metastatic cancer) or in a Canadian setting. This is consistent with a CADTH review from 2012 on the cost-effectiveness of denosumab and zoledronic acid for patients with postmenopausal osteoporosis who have discontinued oral bisphosphonates or are experiencing further decline while on treatment with oral bisphosphonates, which likewise did not identify any relevant studies with this population for inclusion.[18]

The cost-utility analysis submitted by the manufacturer of denosumab in 2011 for the original CDR evaluation of denosumab for the treatment of postmenopausal women with osteoporosis did not provide a comparison with zoledronic acid. The updated 2015 CDEC recommendations regarding denosumab for this indication considered direct and indirect evidence of clinical effectiveness, although uncertainty about the relative effectiveness remained, and CDEC relied on a cost analysis rather than a cost-utility analysis. This cost analysis showed that a 54% reduction in the price of denosumab would be required for cost neutrality with generic zoledronic acid.[10]

CDR was limited to a review of the evidence available in the public domain.[11] CDR also identified the CEA by Parthan et al.;[14] however, the CDR report also cited applicability concerns about the uncertainty regarding assumptions of similar clinical efficacy of denosumab in men and women, the generalizability of osteoporosis in male populations between Sweden and Canada, and concerns about industry sponsorship for the study.[19] The same cost-analysis was presented in this report, which showed that the price of denosumab would require a 54% reduction to reach cost neutrality with generic zoledronic acid.[19]

The current review identified one CEA by Silverman et al.[13] in addition to the CEA by Parthan et al.[14] that was reviewed by CDR in 2015. However, both analyses were based on the same model, conducted by the same authors, and consequently subject to similar limitations. Therefore, this report should be considered in the context of existing CADTH reviews and CDEC recommendations.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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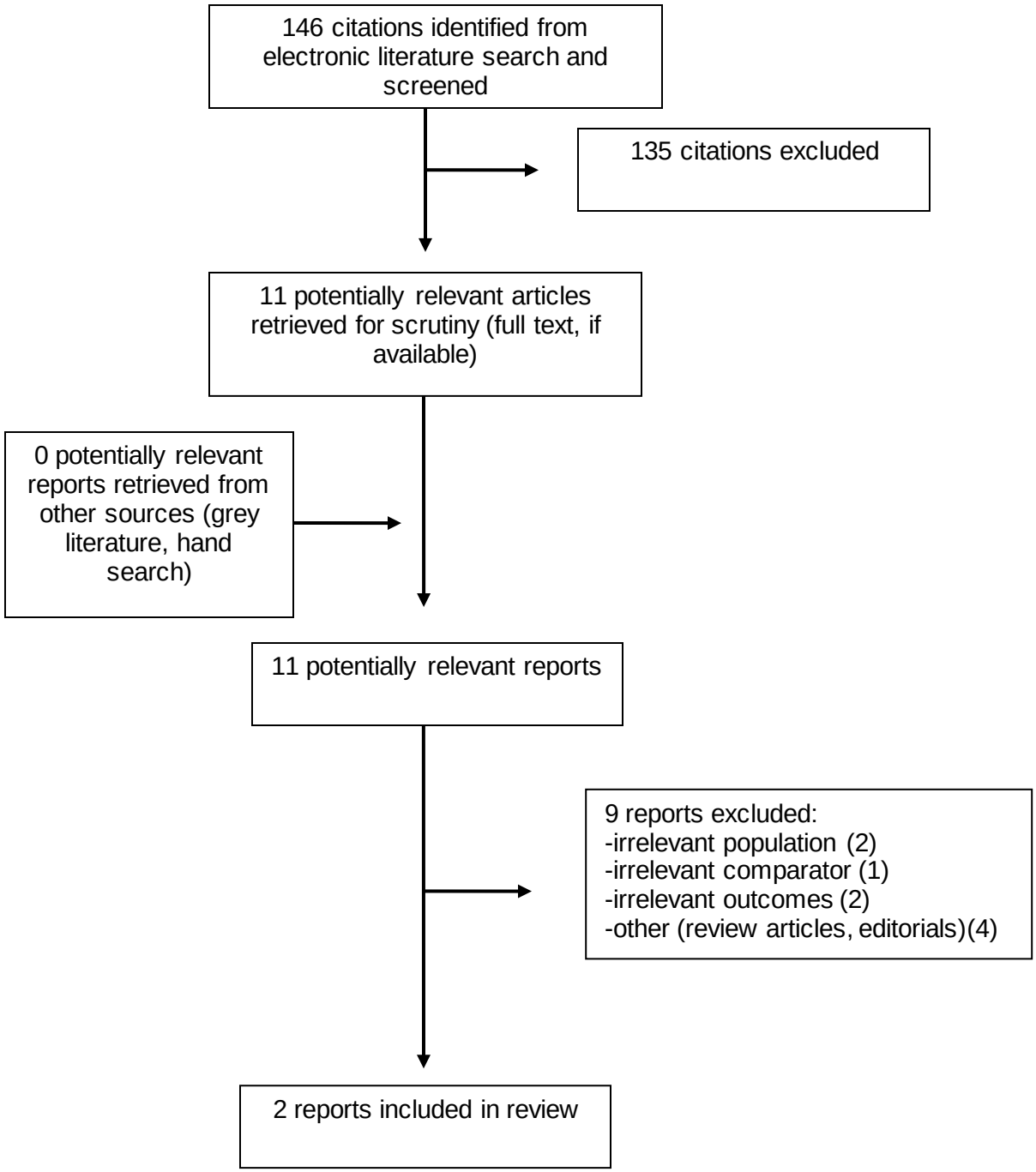
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Intervention, Comparator	Study Population	Main Assumptions
Silverman, 2015,[13] USA	Cost-effectiveness analysis cohort Markov model, lifetime time horizon USA payer perspective	Intervention: denosumab 60 mg every six months Comparators: bisphosphonates (including zoledronic acid), teriparatide Treatment for up to 5 years (teriparatide for 2 years)	Men ≥ 75 years old with osteoporosis	• Fracture risk reduction in men assumed to be comparable to that for postmenopausal women • 0% fracture risk reduction assumed for treatments in absence of any evidence for a particular skeletal site • Injectable treatments (zoledronic acid, teriperatide) assumed to have same adherence rates as denosumab • Offset time (duration of anti-fracture effectiveness after end of treatment) assumed to be 2 years; offset time could not exceed duration of treatment • Mortality would be higher within first year following hip and vertebral fractures than in subsequent years • Costs of nursing home care (hip fractures only) for men estimated from costs for women
Parthan, 2013,[14] USA	Cost-effectiveness analysis cohort Markov model, lifetime time horizon Swedish payer perspective	Intervention: denosumab 60 mg every six months Comparators: bisphosphonates (including zoledronic acid), teriparatide, strontium ranelate Treatment for up to 5 years (teriparatide for 2 years)	Men ≥ 75 years old with osteoporosis	• Fracture risk reduction in men assumed to be comparable to that for postmenopausal women • 0% fracture risk reduction assumed for treatments in absence of any evidence for a particular skeletal site • Constant morphometric vertebral fracture risk assumed in absence of age-specific data • Injectable treatments (zoledronic acid, teriperatide) assumed to have same adherence rates as denosumab; adherence of at least six months assumed • Offset time (duration of anti-fracture effectiveness after end of treatment) assumed to be 2 years; offset time could not exceed duration of treatment • Mortality would be higher within first year following hip and vertebral fractures than in subsequent years • Patients in LTC remained there for the rest of their lives • Patients with non-hip fractures assumed not to be associated with other long-term costs

LTC = long-term care; USA = United States of America.

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Economic Studies using Drummond[12]

Strengths	Limitations
Silverman, 2015[13]	
• Clearly reported research question with related economic importance provided • Clearly described interventions and relevant comparators • Clearly stated and justified choice of economic analysis, perspective, and time horizon • Sources of effect estimates provided and reasonable efficacy assumptions used in absence of evidence • Clearly stated primary outcome measures for the economic evaluation • Sources of utilities, resource use, and costs provided • Quantities or frequency of resource use provided • Costs adjusted for inflation to 2013 American dollar costs where necessary • Markov model described and justified • Approach to sensitivity analyses were described and justified, including choice of variables and range of variation • Incremental analysis is reported • Major outcomes are reported in disaggregated as well as aggregated form • Study question was answered, with conclusions following from the data reported and appropriate caveats added	• Details of the design and results of studies providing effectiveness estimates not described • Details of studies from which utilities derived were not described • Unclear whether long-term care stay after hip fracture was assumed to be permanent in the model • Clinical effectiveness outcomes based on indirect evidence (bone mineral density rather than fracture risk; fracture incidence estimated based on data from postmenopausal women) • Discount rate was stated but not justified
Parthan, 2013[14]	
• Clearly reported research question with related economic importance provided • Clearly described interventions and relevant comparators • Clearly stated and justified choice of economic analysis, perspective, and time horizon • Sources of effect estimates provided and reasonable efficacy assumptions used in absence of evidence • Clearly stated primary outcome measures for the economic evaluation • Sources of utilities, resource use, and costs provided • Source of utilities described and	• Details of the design and results of studies providing effectiveness estimates not described • Clinical effectiveness outcomes based on indirect evidence (bone mineral density rather than fracture risk; fracture incidence estimated based on data from postmenopausal women) • Discount rate was stated but not justified

Table A2: Strengths and Limitations of Economic Studies using Drummond[12]	
Strengths	**Limitations**
appropriate (normal Swedish men) • Quantities or frequency of resource use provided • Costs adjusted for inflation to 2012 euros where necessary • Markov model described and justified • Approach to sensitivity analyses were described and justified, including choice of variables and range of variation • Incremental analysis is reported • Major outcomes are reported in disaggregated as well as aggregated form • Study question was answered, with conclusions following from the data reported and appropriate caveats added	

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td colspan="2">Silverman, 2015[13]</td></tr>
<tr><td>
Base case
<table>
<tr><th></th><th>Cost</th><th>LYs</th><th>QALYs</th></tr>
<tr><td>Denosumab</td><td>$32,334</td><td>7.9339</td><td>6.0386</td></tr>
<tr><td>Zoledronic acid</td><td>$35,138</td><td>7.9132</td><td>6.0037</td></tr>
<tr><td>Incremental</td><td>$2,804</td><td>–0.0208</td><td>–0.0350</td></tr>
</table>
• Generic alendronate had lowest costs in multi-way CEA, followed by denosumab
• Denosumab dominated zoledronic acid (lower costs, higher LYs and QALYs per patient)
• Denosumab ICERs (versus generic alendronate reference): cost per LY saved = $26,389; cost per QALY gained = $16,888
Sensitivity analyses
• Denosumab dominated zoledronic acid when using generic zoledronic acid pricing (35% reduction of base case cost) and alternate offset times
• 85.8% probability of denosumab being cost-effective compared with other treatments at a threshold of $100,000/QALY
</td><td>• Denosumab is a cost-effective option compared with alternative treatments for elderly men with osteoporosis in the United States</td></tr>
<tr><td colspan="2">Parthan, 2013[14]</td></tr>
<tr><td>
Base case
<table>
<tr><th></th><th>Cost</th><th>LYs</th><th>QALYs</th></tr>
<tr><td>Denosumab</td><td>€31,004</td><td>7.4708</td><td>5.2343</td></tr>
<tr><td>Zoledronic acid</td><td>€34,796</td><td>7.4311</td><td>5.1721</td></tr>
<tr><td>Incremental</td><td>€3,792</td><td>–0.0397</td><td>–0.0622</td></tr>
</table>
• Denosumab had lowest costs in multi-way CEA
• Denosumab dominated all comparators (lower costs, higher LYs and QALYs per patient)
Sensitivity analyses
• ICERs (versus generic alendronate) sensitive to the risk of hip fracture with denosumab; RR of hip fracture with denosumab = 0.38 (base case; denosumab dominant), RR = 0.78 (sensitivity analysis; ICER = €39,600/QALY)
• Denosumab dominated zoledronic acid when using generic zoledronic acid pricing (75% reduction of base case cost) and alternative zoledronic acid efficacy data
• 96.1% probability of denosumab being cost-effective compared with other treatments at a threshold of €66,000/QALY
</td><td>• Denosumab is a cost-effective option compared with alternative treatments for elderly men with osteoporosis in Sweden</td></tr>
</table>

CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year; RR = relative risk.