EXPERT REVIEWS

Cost–effectiveness of denosumab in the treatment of postmenopausal osteoporotic women

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Denosumab is a novel biological agent for the treatment of osteoporosis in postmenopausal women with increased risk of fractures. With limited healthcare resources, economic evaluations are increasingly being used by decision-makers to optimize healthcare resource allocation. The cost–effectiveness of denosumab has been evaluated in various studies, and a systematic literature study was conducted up to April 2012 to identify all published research articles and research abstracts presented at various congresses. This article provides a systematic review of four articles and eight abstracts reporting on the cost–effectiveness of denosumab in the treatment of osteoporosis. In most economic evaluations, denosumab has been considered as a cost-effective treatment compared with first-line and second-line options (including generic alendronate) in the treatment of women with high risk of fractures.

Keywords: cost–effectiveness • denosumab • osteoporosis

Osteoporosis is an increasingly major public health problem around the world. It is estimated that, in western countries, one in three women and one in five men over the age of 50 years will experience an osteoporotic fracture during their remaining lifetime [1]. Osteoporotic fractures result in significant morbidity, excess mortality and reduction in quality of life [2–4]. They also impose a financial burden on healthcare systems. In six major European countries, the burden of osteoporotic fractures in 2010 was estimated to be at €31 billion [5].

Oral bisphosphonates have been the most widely prescribed drugs for the treatment and prevention of osteoporosis, with demonstrated efficacy in reducing the risks of vertebral and nonvertebral fractures [6]. However, effectiveness in real-life settings is jeopardized by poor adherence. Several studies have reported that between 50 and 75% of women who initiate oral bisphosphonates are nonadherent within 1 year [7,8], and that the majority of patients with hip fractures did not receive any medication [9–11]. Poor adherence reduces the effectiveness of osteoporosis treatment, increasing fracture rates [12]. Approximately 50% of the potential clinical benefits of oral bisphosphonates are expected to be lost owing to nonadherence and this reduces the cost–effectiveness of osteoporosis medications [13–15].

Denosumab is a novel agent for the treatment of osteoporosis in postmenopausal women with increased risk of fractures. In a 3-year randomized clinical trial including postmenopausal women with osteoporosis, subcutaneous injection of denosumab every 6 months significantly reduced the risk of hip, vertebral and nonvertebral fractures [16]. An attractive feature of the 6-month regimen with denosumab is that adherence may be improved compared with weekly regimens, thereby improving effectiveness in real-life settings and preventing more fractures [17]. Recently, a 2-year randomized open-label study indeed demonstrated significantly greater treatment adherence and persistence for subcutaneous injection of denosumab every 6 months compared with oral alendronate once weekly [18,19]. Risk ratios for denosumab compared with alendronate at 12 months were estimated at 0.58 for nonadherence ($p = 0.043$) and 0.54 for nonpersistence ($p = 0.049$) [19].

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With the introduction of new (and more expensive) treatments, the economic value of newer agents compared with existing alternatives needs to be assessed. Health–economic evaluations have become increasingly important to support priority settings in healthcare and help decision-makers to efficiently allocate healthcare resources. It is therefore not surprising that studies on the cost–effectiveness of denosumab have been recently performed. Understanding the different aspects of the evidence of cost–effectiveness of denosumab would be very useful for healthcare decision-making and also to identify gaps in the current evidence that could inform future economic evaluations. This study was therefore designed to systematically review and critically appraise existing economic evaluations of denosumab for the treatment of postmenopausal osteoporotic women.

Methods

Search strategy

A systematic literature search was conducted to find all published research articles and research abstracts presented in various congresses. The literature search was conducted using databases such as Medline, Centre for Reviews and Dissemination databases, Cost–effectiveness Analysis Registry and the Cochrane Library for articles up to 30 April 2012. In addition, congress abstracts were searched directly from four congress organizers: the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the European Congress for Clinical and Economic Aspects of Osteoporosis, the International Osteoporosis Foundation and the American Society for Bone and Mineral Research. Abstracts presented at the ISPOR Annual International Meeting in June 2012 were also searched. For the ISPOR abstracts, the related congress posters were searched on the congress website.

The following search terms were used: denosumab AND (cost–effectiveness or cost–utility or economic or evaluation or cost) for research articles and the term 'denosumab' was used to find congress abstracts. Evaluation reports from the manufacturer or from different national agencies were not searched. Nevertheless, formal Health Technology Assessment (HTA) reports are covered by the searched HTA database, and these were not excluded if found in the database search. Editorials or comments were excluded. The search was also restricted to English-language literature.

Selection of studies

The authors included full economic evaluation of denosumab (in one of the treatment arms) for the treatment of postmenopausal women with osteoporosis. A full economic evaluation was defined as the comparison of costs and outcomes, including cost–effectiveness analyses, in which results are usually expressed as cost per unit of effect (e.g., cost per fracture prevented gained), and cost–utility analyses, in which results are generally expressed as a cost per quality-adjusted life year (QALY) gained [20]. Two reviewers (Hiligsmann and Ben Sedrine) independently applied these criteria to identify citations during title and abstract screening. Reference lists of identified economic evaluation were also manually searched. Congress abstracts that were published as full articles and duplicate abstracts reporting the same data were excluded.

Data extraction & critical appraisal

Data were extracted using a standard collection form. The extracted study characteristics from articles were based on the following: study design (country, perspective, outcome measure, model type, time horizon, price year, discount rates and funding), population, comparator and treatment characteristics (efficacy source, adherence, treatment duration, offset time and drug cost) and study outcomes (results and sensitivity analyses). Reported incremental cost–effectiveness ratios (ICERs) were presented in Euros, British pounds or US dollars; no other adjustments were made. A simple extraction form was used to extract information for congress abstracts including congress name, year/month, country, perspective, model, population, comparator, ICER and funding. Two reviewers (Hiligsmann and Ben Sedrine) independently extracted data from articles and congress abstracts.

Quality of selected articles were appraised with the British Medical Journal (BMJ) checklist [21] by two independent reviewers (Boonen and Dirksen), not being authors of any of the original articles. Thirty five items related to study design, data collection, analysis and interpretation of results were scored using 'Yes', 'No', 'Not Clear', 'Substandard' and 'Not Applicable'. Discrepancies in rating were resolved by consensus and a third reviewer (Hiligsmann) was consulted to reconcile disagreements. The methodological quality of the congress abstracts was not evaluated.

Results

The initial database search identified 72 research articles and 113 congress abstracts, of which 18 articles were excluded as duplicates (Figure 1). The authors reviewed all titles and abstracts of these articles, and subsequently excluded 50 research articles and 105 congress abstracts that did not meet our inclusion criteria. Four abstracts were excluded because they were published as full articles [22–25] and one abstract was a duplicate result [26]. A total of four research articles [17,27–29] and eight congress abstracts [30–37] fulfilled our inclusion criteria. Among the published articles, three of these were 'original research' [17,27,28] (funded by the manufacturer of denosumab, Amgen) and the last one provided a description of a dossier submitted by Amgen in the UK and the subsequent NICE appraisal [29,38].

Selected articles

Two studies were conducted in Belgium [27,28], one in Sweden [17] and one in the UK (Table 1) [29]. Economic perspectives included societal (n = 1) [17] and healthcare payer (n = 3) [27–29]. All studies used a lifetime time horizon and were Markov models with QALY as the outcome measure. Markov models were analyzed using a cohort-based approach [17,29] or an individual patient simulation [27,28]. Discount rates varied between studies and were based on local guidelines for economic evaluations. Three studies were funded by the manufacturer of denosumab [17,27,28], and the last

one was a review of the manufacturer submission to the NICE in the UK and the NICE appraisal funded by a UK HTA program [29].

Efficacy data from the FREEDOM Trial that was published in 2009 were used in all studies [16]. Treatment duration in modeling was assumed for a maximum of 3 [27,28] or 5 years [17,29], although all models used a lifetime horizon to capture the long-term effects of preventing fractures. Adherence to denosumab was included in the base case in only two studies [17,28]. For the main comparators, Hiligsmann and Reginster [28] incorporated both compliance and persistence, while Jönsson *et al.* [17] only included medication persistence. Treatment duration was assumed to linearly decline to zero after stopping therapy, for a maximum of 1 year [27–29] or over the same period as the time on treatment [17]. Two studies used the same assumption for denosumab and the comparators [17,29], while the effect of denosumab after stopping therapy was conservatively assumed to be shorter compared with the alternatives in another study [28]. None of the studies included side effects for denosumab, as the clinical trial reported no significant differences in the total incidence of adverse events and serious adverse events between subjects who received denosumab and those who received placebo [16]. In addition to drug cost (estimated at €415 [27,28], €425 [17] and GB£366 [29] per year), all studies incorporated the cost of two yearly visits to general physicians (GPs) in the base case. However, the Evidence Review of Group (ERG) commissioned by the NICE expressed concerns about this assumption, suggesting that denosumab might be flagged for administration and monitoring in secondary care only [29]. Nevertheless, assuming one dose of denosumab administrated per year in secondary care had a limited impact on the cost–effectiveness of denosumab [29].

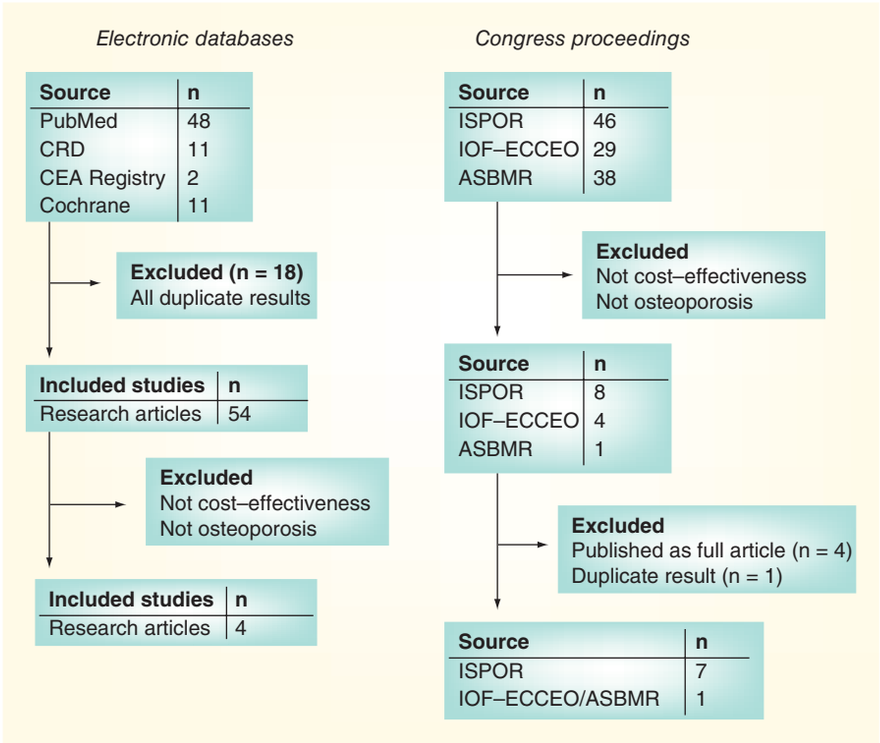

Figure 1. Literature search flow chart (electronic databases and congress proceedings).
ASBMR: American Society for Bone and Mineral Research; CEA: Cost–effectiveness analyses; CRD: Centre for Reviews and Dissemination; IOF–ECCEO: The International Osteoporosis Foundation–European Congress for Clinical and Economic Aspects of Osteoporosis; ISPOR: International Society for Pharmacoeconomics and Outcomes Research.

Out of the four articles, 14 comparisons were performed between denosumab and alternative treatment. Comparator treatments included no treatment (n = 3), generic alendronate (n = 2), branded alendronate (n = 1), ibandronate (n = 1), raloxifene

Table 1. Characteristics of published articles assessing the cost–effectiveness of denosumab in the treatment of osteoporosis.

Study (year)	Country	Perspective	Outcome measure	Model type	Time horizon	Currency, year	Discount rates (cost, QALY)	Funding	Ref.
Hiligsmann and Reginster (2010)	Belgium	Healthcare payer	QALYs	Markov: microsimulation	Lifetime	€, 2009	3–1.5%	Amgen	[27]
Hiligsmann and Reginster (2011)	Belgium	Healthcare payer	QALYs	Markov: microsimulation	Lifetime	€, 2009	3–1.5%	Amgen	[28]
Jönsson *et al.* (2011)	Sweden	Societal	QALYs	Markov: cohort	Lifetime	€, 2008	3–3%	Amgen	[17]
Scotland *et al.* (2011)	UK	UK health and social care perspective	QALYs	Markov: cohort	Lifetime	GB£, 2009	3.5–3.5%	NIHR HTA – Amgen	[29]

QALY: Quality-adjusted life year.

Table 2. Results of published articles assessing the cost–effectiveness of denosumab in the treatment of osteoporosis.

Study (year)	Population	Comparator	Results (ICER of denosumab vs comparator treatment)	Ref.
Hiligsmann and Reginster (2010)	FREEDOM trial[†] Women with BMD T-score ≤–2.5 and no prior fracture	No treatment No treatment	€28,441 €25,061 (60 years), €8948 (70 years), €642 (80 years)	[27]
Hiligsmann and Reginster (2011)	Women aged 70 years with BMD T-score ≤-2.5 and no prior fracture Women aged 70 years with prevalent vertebral fracture	Generic alendronate Branded alendronate Branded risedronate Generic alendronate Branded alendronate Branded risedronate	€22,220 €14,120 €-209 €14,166 €19,718 €4456	[28]
Jönsson *et al.* (2011)	Typical Swedish patient population[‡]	Generic alendronate Risedronate Strontium ranelate No treatment	€27,090 €11,545 €5015 €14,458	[17]
Scotland *et al.* (2011)	Women aged 70 years with a T-score of -2.5 or less and no prior fracture Women aged 70 years with a T-score of -2.5 or less with a prior fragility fracture	Strontium ranelate Raloxifene No treatment ZoL Intravenous ibandronate Teriparatide (PTH) Strontium ranelate Raloxifene No treatment ZoL Intravenous ibandronate Teriparatide (PTH)	Dominant GB£9289 GB£29,223 ICER of ZoL[§]: GB£70,900 Dominant ICER of PTH[§]: GB£772,424 Dominant GB£2000 GB£12,381 ICER of ZoL[§]: GB£29,029 Dominant ICER of PTH[§]: GB£451,269	[29]

ICERs are expressed in cost per QALY gained.
[†]Women aged 72 years, T-score of -2.2 and 23.6% of those had prevalent vertebral fracture.
[‡]Women aged 71 years, T-score ≤-2.5 and a prevalence of morphometric vertebral fractures of 34%.
[§]Incremental cost–effectiveness ratio of zoledronic acid or of teriparatide compared with denosumab.
BMD: Bone mineral density; ICER: Incremental cost–effectiveness ratio; PTH: Parathyroid hormone; ZoL: Zoledronic acid.

(n = 1), risedronate (n = 2), strontium ranelate (n = 2), teriparatide (n = 1) and zoledronic acid (n = 1).

Results of the cost–effectiveness literature of denosumab are reported in Table 2. Overall, the ICER of denosumab falls below commonly accepted thresholds for cost–effectiveness. Although, in most countries, there are no generally accepted or recommended thresholds for cost–effectiveness, interventions with cost per QALY gained lower than €30,000–60,000 were usually considered as 'good value for money' in treating osteoporosis [39,40]. Using a Belgian healthcare payer perspective, denosumab was deemed to be cost effective compared with no treatment in patients with similar characteristics to those included in the FREEDOM trial and in a population of patients that would be eligible to receive treatment in many European countries based on osteoporosis medication reimbursement guidelines, that is, with bone mineral density T-score ≤-2.5 or prevalent vertebral fracture [27]. The same authors further assessed the cost–effectiveness of denosumab compared with the most relevant alternatives (i.e., branded and generic oral bisphosphonates) [28]. The analysis demonstrated that denosumab was cost effective compared with oral bisphosphonates (including generic alendronate) in the treatment of postmenopausal women with osteoporosis aged over 60 years, assuming a willingness to pay €40,000 per QALY gained. A sensitivity analysis suggested that results were influenced by adherence to oral bisphosphonates and fracture risk. In a Swedish setting using a societal perspective, denosumab was also shown to be cost effective compared with generic alendronate, risedronate and strontium ranelate for typical Swedish women receiving osteoporosis medications [17]. In the UK, the cost–effectiveness of denosumab was demonstrated compared with no treatment, strontium ranelate, raloxifene, intravenous ibandronate and teriparatide [29]. The cost–effectiveness of denosumab versus zoledronic acid, which was considered by the ERG as the main comparator, is however uncertain, and is sensitive to the assumptions associated with the costs of administration of denosumab (i.e., two GP visits per year or one dose of denosumab per year in secondary care). The ERG found it difficult to separate denosumab and zoledronic acid on grounds of cost–effectiveness in the UK [29]. Table 3 presents the appraisal of the original studies on the cost–effectiveness of denosumab (except the NICE appraisal) using the BMJ criteria [29]. Published articles are based on good-quality models that have been previously validated [41,42]. Study design was generally clearly described. However, studies did not describe quantities of resource use separately from their unit costs,

Table 3. Results of quality appraisal of articles assessing the cost–effectiveness of denosumab: *British Medical Journal* criteria.

British Medical Journal criteria	Hiligsmann and Reginster (2010) [27]	Hiligsmann and Reginster (2011) [28]	Jönsson *et al.* (2011) [17]
Study design			
1 – The research question is stated	Yes	Yes	Yes
2 – The economic importance of the research question is stated	Sub	Yes	Yes
3 – The viewpoint(s) of the analysis is (are) clearly stated and justified	Yes	Yes	Yes
4 – The rationale for choosing alternative programs or interventions compared is stated	Yes	Yes	Yes
5 – The alternatives being compared are clearly described	Yes	Yes	Yes
6 – The form of the economic evaluation used is stated	Yes	Yes	Yes
7 – The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	Yes	No
Data collection			
8 – The source(s) of effectiveness estimates used is (are) stated	Yes	Yes	Yes
9 – Details of the design and results of effectiveness study are given (if based on a single study)	NA	NA	NA
10 – Details of methods of synthesis or meta-analysis of estimates are given	NA	NA	NA
11 – The primary outcome measures(s) for the economic evaluation are clearly stated	Yes	Yes	Yes
12 – Methods to value benefits are stated	Sub	Sub	Yes
13 – Details of subjects from whom valuations were obtained were given	Sub	Yes	Yes
14 – Productivity changes (if included) are reported separately	NA	NA	No
15 – The relevance of productivity changes to the study question is discussed	No	No	No
16 – Quantities of resource use are reported separately from their unit costs	Sub	Sub	Sub
17 – Methods for the estimation of quantities and unit costs are described	No	Sub	No
18 – Currency and price data are recorded	Yes	Yes	Yes
19 – Details of currency of price adjustments for inflation or currency conversion are given	Yes	Yes	Yes
20 – Details of any model used are given	Yes	Yes	Yes
21 – The choice of model used and the key parameters on which it is based are justified	Yes	Yes	Yes
Analysis and interpretation of results			
22 – Time horizon of costs and benefits is stated	Yes	Yes	Yes
23 – The discount rate(s) is (are) justified	Yes	Yes	Yes
24 – The choice of discount rate(s) is (are) justified	Yes	Yes	Yes
25 – An explanation is given if costs and benefits are not discounted	NA	NA	NA
26 – Details of statistical tests and confidence intervals are given for stochastic data	Yes	Yes	No
27 – The approach to sensitivity analysis is given	Yes	Yes	Sub
28 – The choice of variables for sensitivity analysis is justified	Sub	Sub	No
29 – The ranges over which the variables are varied are justified	Sub	Sub	No

NA: Not applicable; Sub: Substandard.

Table 3. Results of quality appraisal of articles assessing the cost–effectiveness of denosumab: British Medical Journal criteria (cont.).

British Medical Journal criteria	Hiligsmann and Reginster (2010) [27]	Hiligsmann and Reginster (2011) [28]	Jönsson *et al.* (2011) [17]
Analysis and interpretation of results (cont.)			
30 – Relevant alternatives are compared	Sub	Sub	Sub
31 – Incremental analysis is reported	Yes	Yes	Yes
32 – Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Yes	Yes
33 – The answer to the study question is given	Yes	Yes	Yes
34 – Conclusions follow from the data reported	Yes	Yes	Yes
35 – Conclusions are accompanied by the appropriate caveats	Yes	Yes	Yes

NA: Not applicable; Sub: Substandard.

probably because in models no original costing studies were done but costs related to these events were derived from other sources. All studies reported incremental analyses, and major outcomes were presented in a disaggregated and aggregated form. Only two studies reported stochastic data and performed probabilistic sensitivity analyses [27,28], while the choice of variables for sensitivity analyses and the range over which they are varied were not fully reported.

Selected abstracts

Most of the included congress abstracts (seven out of eight) were presented at different ISPOR meetings between 2009 and 2012. One study was presented at The International Osteoporosis Foundation–European Congress for Clinical and Economic Aspects of Osteoporosis meeting. From the seven included ISPOR abstracts, the related congress posters were available in four cases [31,32,35,37]. Five abstracts were funded by the manufacturer of denosumab and three did not provide information about funding sources.

Characteristics and results from these abstracts are reported in Table 4. Research was conducted by eight different authors in six different countries. Abstracts during 2009–2011 provided further evidence on the cost–effectiveness of denosumab in other European settings, suggesting that denosumab is also cost effective compared with current treatment options in Greece, Portugal, Scotland, Spain and the UK [30,31,35–37].

Recently, three abstracts reported on the cost–effectiveness of denosumab in the USA at the ISPOR Annual International Meeting in June 2012, with contrasting results. Based on a previously validated model, Parthan *et al.* showed that denosumab represented a good value for money treatment compared with branded bisphosphonates in the overall postmenopausal population and was either cost effective or dominant compared with generic alendronate in the higher risk subgroups [32]. Jiang and Hay also compared denosumab and generic alendronate in the USA using a new type of model and concluded that denosumab was not cost effective [33]. Finally, Beaubrun and Daugherty suggested that denosumab was not cost effective compared with raloxifene [34]. Unfortunately, posters were not available for these last two congress abstracts, and only limited information was available on the new model structure and the efficacy data used in the abstract, making it difficult to assess the quality of these evaluations.

Expert commentary

Denosumab represents a new therapeutic option for the treatment of postmenopausal women at high risk of fractures. The cost–effectiveness of denosumab in this indication has been assessed against multiple treatments in several studies. In these analyses, denosumab has been considered to be cost effective compared with most treatment options (including oral treatments). The cost–effectiveness of denosumab versus once-yearly injection of zoledronic acid remains, however, uncertain, depending mainly on assumptions about the costs of administration of denosumab.

This review identified four published articles based on good-quality models and eight additional congress abstracts that estimated the cost–effectiveness of denosumab in the treatment of postmenopausal osteoporotic women. Published articles were only conducted in three European countries (Belgium, Sweden and the UK). Congress abstracts suggest that denosumab is likely to be cost effective in other European countries with similar characteristics. The transferability of economic evaluations across jurisdictions could, however, be uncertain, as differences in the incidence of disease, availability of health resources, clinical practice patterns and relative prices may impact cost–effectiveness [43]. Recently, research abstracts about the cost–effectiveness of denosumab in the USA were presented at the ISPOR congress (2012), and we could therefore expect full articles in non-European countries in the near future.

Other gaps were identified. First, adherence and persistence with osteoporosis medications were not incorporated in all studies, despite their potential impact on the cost–effectiveness results [13,44]. In particular, when comparing drugs with potential differences in adherence and persistence (e.g., denosumab vs oral drug treatment), the lack of inclusion of these concepts could bias the results and lead to suboptimal allocation of resources [13]. Recently published data on adherence and persistence to denosumab compared with alendronate would definitely be interesting

Table 4. Characteristics and results of congress abstracts assessing the cost–effectiveness of denosumab in the treatment of osteoporosis.

Study (year)	Congress	Country	Perspective	Population	Comparators	ICER of denosumab vs comparator	Funding	Ref.
Ström *et al.* (2009)	ASBMR and IOF–ECCEO	UK	Healthcare payer	Women aged 70 years with BMD T-score of -2.5	Risedronate Placebo	GB£14,300 GB£10,700	Amgen	[30]
Cristino *et al.* (2011)	ISPOR	Portugal	National health service	NR	Alendronate–colecalciferol	€14,487	NR	[36]
Davies *et al.* (2011)	ISPOR	Scotland	National health service	Women aged 70 years with BMD T-score of -2.5 (and no prior fracture)	Strontium ranelate Ibandronate Raloxifene No treatment ZoL	Dominant Dominant GB£4,339 GB£22,380 GB£120,000	Amgen	[31]
Darba *et al.* (2011)	ISPOR	Spain	National healthcare system	Women aged 65 years with BMD T-score of -2.5 and a prevalence of morphometric vertebral fractures of 36%	No treatment Generic alendronate Generic risedronate Ibandronate Strontium ranelate	€17,345 €15,397 €14,543 Dominant Dominant	Amgen	[35]
Athanasakis *et al.* (2011)	ISPOR	Greece	Third party payer	FREEDOM trial	No treatment Alendronate Ibandronate Risedronate Strontium ranelate	€18,813 €24,784 €13,727 €18,436 €11,114	Amgen	[37]
Parthan *et al.* (2012)	ISPOR	USA	Third party payer	High-risk subgroups (overall PMO population)	Risedronate Ibandronate Generic alendronate	Dominant (NR) Dominant (Dominant) US$28,200 (US$103,000)	Amgen	[32]
Jiang and Hay (2012)	ISPOR	USA	Societal	Not clear	Generic alendronate	US$2,111,647	NR	[33]
Beaubrun and Daugherty (2012)	ISPOR	USA	Managed care	Women aged over 65 years with BMD T-score ≤-2.5	Raloxifene	Dominated	NR	[34]

ASBMR: American Society for Bone and Mineral Research; BMD: Bone mineral density; ICER: Incremental cost–effectiveness ratio; IOF–ECCEO: International Osteoporosis Foundation–European Congress on Osteoporosis and Osteoarthritis; ISPOR: International Society For Pharmacoeconomics and Outcomes Research; NR: Not reported; PMO: Postmenopausal osteoporosis; ZoL: Zoledronate.

for further cost–effectiveness analyses of denosumab [18,19]. There are also some investigations of denosumab in particularly high-risk patients, suggesting a better cost–effectiveness profile of this drug in this particular clinical condition [45,46].

Second, no direct comparisons between denosumab and other treatments are currently available. Indirect comparisons of efficacy between drugs are less robust because of different baseline characteristics of the populations studied and overlapping confidence intervals for the effect of treatment [47]. Further research would therefore be required to confirm the findings, ideally with head-to-head observational studies of denosumab compared with oral bisphosphonates, to provide more robust data. Further studies are also required to evaluate adverse events and long-term safety of denosumab in real-world clinical practice that could potentially be included in further cost–effectiveness analyses.

Further investigation is also needed to assess the effect of denosumab after stopping therapy. Recent data suggest that the treatment benefit achieved (changes in bone mineral density) with 2 years of denosumab therapy was reversed within 2 years of treatment discontinuation, and remained above those of the group previously treated with placebo [48]. However, there is no consensus on this effect, including potential differences with other osteoporotic treatments. Another issue is the monitoring costs of denosumab. Existing economic evaluations incorporated the cost of two yearly visits to GPs, but the ERG in the UK expressed concerns about this assumption, suggesting that

denosumab might be flagged for administration and monitoring in secondary care only. Finally, assessing the value of perfect information would be useful to inform policy decisions about future research in this topic [49].

We followed recommendations for conducting reviews of economic evaluations [50]. Two independent reviewers were used for literature search, data extraction and quality assessment. Critical appraisal of published articles was done by two authors, who were not authors of the original articles, using the BMJ checklist, as recommended [50]. Some discrepancies were observed between reviewers, but were only a matter of interpretation. The critical appraisal of congress abstracts is not meaningful, as too little information is included in congress abstracts, which must therefore be interpreted with the greatest caution.

Most studies included in this review were funded by the manufacturer of denosumab: three published articles out of the four and five of the eight congress abstracts. However, as reported in a case study in bisphosphonates, the funding source did not seem to significantly affect the reporting of low or high ICERs in the treatment of osteoporosis [51]. In addition, models used in funding studies were previously validated and have been used to assess the cost–effectiveness of other osteoporosis medications [41,42].

Five-year view

Poor adherence to therapy represents a major problem in the treatment of osteoporosis. Improving medication adherence is becoming urgently needed, and the use of longer dosing regimens could be an effective way to enhance medication adherence. Administered as a subcutaneous injection every 6 months, denosumab is a novel attractive drug for the treatment of osteoporosis. Denosumab also represents a cost-effective alternative compared with existing oral osteoporosis treatments, and may be considered as a first-line treatment option for patients at high risk of fracture. As a future standard of treatment, it is likely that there will be a number of cost–effectiveness articles of denosumab in the future. In particular, one would expect cost–effectiveness articles of denosumab in non-European countries, as well as using real-world adherence and effectiveness data.

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Key issues

- Denosumab is a novel agent for the treatment of osteoporosis in postmenopausal women, demonstrating efficacy in reducing the risk of hip, vertebral and nonvertebral fractures.
- The cost–effectiveness of denosumab in the treatment of postmenopausal women with osteoporosis has been evaluated in various published research articles and abstracts presented at various congresses.
- In most economic evaluations, denosumab has been deemed to be cost effective compared with first- and second-line drug therapies in the treatment of postmenopausal women with high risk of fractures.
- Further articles on the cost–effectiveness analyses of denosumab are expected in non-European countries and using real-world adherence and effectiveness data.

References

Papers of special interest have been highlighted as:
• of interest
•• of considerable interest

1 Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C; IOF Working Group on Epidemiology and Quality of Life. A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos. Int.* 23(9), 2239–2256 (2012).

2 Haentjens P, Magaziner J, Colón-Emeric CS *et al.* Meta-analysis: excess mortality after hip fracture among older women and men. *Ann. Intern. Med.* 152(6), 380–390 (2010).

3 Lips P, van Schoor NM. Quality of life in patients with osteoporosis. *Osteoporos. Int.* 16(5), 447–455 (2005).

4 Johnell O, Kanis JA, Odén A *et al.* Mortality after osteoporotic fractures. *Osteoporos. Int.* 15(1), 38–42 (2004).

5 Ström O, Borgström F, Kanis JA *et al.* Osteoporosis: burden, health care provision and opportunities in the EU: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch. Osteoporos.* 6(1–2), 59–155 (2011).

6 Reginster JY. Treatment of postmenopausal osteoporosis. *BMJ* 330(7496), 859–860 (2005).

7 Rabenda V, Hiligsmann M, Reginster JY. Poor adherence to oral bisphosphonate treatment and its consequences: a review of the evidence. *Expert Opin. Pharmacother.* 10(14), 2303–2315 (2009).

8 Siris ES, Selby PL, Saag KG, Borgström F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am. J. Med.* 122(Suppl. 2), S3–S13 (2009).

9 Carnevale V, Nieddu L, Romagnoli E *et al.* Osteoporosis intervention in ambulatory

patients with previous hip fracture: a multicentric, nationwide Italian survey. *Osteoporos. Int.* 17(3), 478–483 (2006).

10 Liel Y, Castel H, Bonneh DY. Impact of subsidizing effective anti-osteoporosis drugs on compliance with management guidelines in patients following low-impact fractures. *Osteoporos. Int.* 14(6), 490–495 (2003).

11 Rabenda V, Vanoverloop J, Fabri V *et al*. Low incidence of anti-osteoporosis treatment after hip fracture. *J. Bone Joint Surg. Am.* 90(10), 2142–2148 (2008).

12 Curtis JR, Yun H, Lange JL *et al*. Does medication adherence itself confer fracture protection? an investigation of the healthy adherer effect in observational data. *Arthritis Care Res. (Hoboken)* 64(12), 1855–1863 (2012).

13 Hiligsmann M, Boonen A, Rabenda V, Reginster JY. The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. *Expert Rev. Pharmacoecon. Outcomes Res.* 12(2), 159–166 (2012).

• **Highlights the importance of incorporating medication adherence in economic evaluations conducted in osteoporosis.**

14 Hiligsmann M, McGowan B, Bennett K, Barry M, Reginster JY. The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland. *Value Health* 15(5), 604–612 (2012).

15 Hiligsmann M, Rabenda V, Bruyère O, Reginster JY. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. *Health Policy* 96(2), 170–177 (2010).

16 Cummings SR, San Martin J, McClung MR *et al*.; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N. Engl. J. Med.* 361(8), 756–765 (2009).

• **Results of the clinical trial of denosumab.**

17 Jönsson B, Ström O, Eisman JA *et al*. Cost–effectiveness of denosumab for the treatment of postmenopausal osteoporosis. *Osteoporos. Int.* 22(3), 967–982 (2011).

•• **Published article on the cost–effectiveness of denosumab.**

18 Freemantle N, Satram-Hoang S, Tang ET *et al*.; DAPS Investigators. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos. Int.* 23(1), 317–326 (2012).

19 Kendler DL, McClung MR, Freemantle N *et al*.; DAPS Investigators. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. *Osteoporos. Int.* 22(6), 1725–1735 (2011).

20 Drummond M, Sculpher M, O'Brien B, Stoddart G, Torrance G. *Methods for the Economic Evaluation of Health Care Programmes (3rd Edition)*. Oxford University Press, New York, NY, USA (2007).

21 Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 313(7052), 275–283 (1996).

22 Hiligsmann M, Reginster J. Cost–effectiveness of denosumab compared with generic alendronate in the treatment of postmenopausal osteoporotic women. *Value Health* 13, A309–A310 (2010).

23 Hiligsmann M, Reginster J. Cost–effectiveness of denosumab compared with generic alendronate in the treatment of postmenopausal osteoporotic women. *Osteoporosis Int*. 22, S112 (2011).

24 Hiligsmann M, Reginster J. Cost–effectiveness of denosumab compared with oral bisphosphonates in the treatment of postmenopausal osteoporotic women. *Osteoporosis Int*. 21, S30 (2010).

25 Hiligsmann M, Reginster J. Cost–utility of denosumab for the treatment of postmenopausal osteoporotic women. *Osteoporosis Int.* 20, S16 (2009).

26 Ström O, Macarios D, Badamgarav E, Borgstrom F, Tosteson A, Kanis J. A UK denosumab cost–effectiveness model incorporating FRAX and Adherence. *J. Bone Miner. Res.* 24, S141 (2009).

27 Hiligsmann M, Reginster JY. Potential cost–effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. *Bone* 47(1), 34–40 (2010).

•• **Published article on the cost–effectiveness of denosumab.**

28 Hiligsmann M, Reginster JY. Cost–effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. *Pharmacoeconomics* 29(10), 895–911 (2011).

•• **Published article on the cost–effectiveness of denosumab.**

29 Scotland G, Waugh N, Royle P, McNamee P, Henderson R, Hollick R. Denosumab for the prevention of osteoporotic fractures in post-menopausal women: a NICE single technology appraisal. *Pharmacoeconomics* 29(11), 951–961 (2011).

•• **Published article on the cost–effectiveness of denosumab.**

30 Ström O, Macarios D, Badamgarav E *et al*. Cost–effectiveness model for denosumab incorporating FRAX and adherence in a UK Setting. *Osteoporosis Int*. 20, S20 (2009).

31 Davies A, Compston J, Ferguson S, McCloskey E, Shearer A, Taylor A. Cost–effectiveness of denosumab in the treatment of postmenopausal osteoporosis in Scotland. *Value Health* 14, A310 (2011).

32 Parthan A, Deflin M, Yurgin N, Huang J, Taylor D. Cost–effectiveness of denosumab versus oral bisphosphonates in the Unites States for post-menopausal osteoporosis. *Value Health* 15, A38 (2012).

33 Jiang Y, Hay J. The cost–effectiveness of denosumab for the prevention of osteoporotic fractures in the setting of the Unites States. *Value Health* 15, A38 (2012).

34 Beaubrun A, Daugherty J. Cost–utility analysis of denosumab versus raloxifene for treating osteoporosis in post-menopausal women in the United States. *Value Health* 14, A129 (2012).

35 Darba J, Kaskens L, Sorio F. Cost–utility of denosumab for the treatment of postmenopausal osteoporosis in Spain. *Value Health* 14, A311 (2011).

36 Cristino J, Canhão H, Perelman J, Santos C, Pereira J. Cost–utility analysis of denosumab versus standard care in the treatment of post-menopausal osteoporosis in Portugal. *Value Health* 14, A128 (2011).

37 Athanasakis K, Karampli E, Hollandezos M *et al*. A cost–effectiveness analysis of denosumab for the treatment of post-menopausal osteoporosis in Greece. *Value Health* 14, A138 (2011).

38 Waugh N, Royle P, Scotland G, Henderson R, Hollick R, McNamee P. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. *Health Technol. Assess.* 15(Suppl. 1), 51–59 (2011).

39 Ström O, Borgström F, Sen SS *et al*. Cost–effectiveness of alendronate in the treatment of postmenopausal women in 9 European countries – an economic evaluation based on the fracture intervention trial. *Osteoporos. Int.* 18(8), 1047–1061 (2007).

40 Tosteson AN, Melton LJ 3rd, Dawson-Hughes B *et al*.; National Osteoporosis Foundation Guide Committee. Cost-effective osteoporosis treatment thresholds:

the United States perspective. *Osteoporos. Int.* 19(4), 437–447 (2008).

41 Hiligsmann M, Ethgen O, Bruyère O, Richy F, Gathon HJ, Reginster JY. Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. *Value Health* 12(5), 687–696 (2009).

42 Zethraeus N, Borgström F, Ström O, Kanis JA, Jönsson B. Cost–effectiveness of the treatment and prevention of osteoporosis – a review of the literature and a reference model. *Osteoporos. Int.* 18(1), 9–23 (2007).

43 Drummond M, Barbieri M, Cook J *et al*. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. *Value Health* 12(4), 409–418 (2009).

44 Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R. Partial adherence: a new perspective on health economic assessment in osteoporosis. *Osteoporos. Int.* 22(10), 2565–2573 (2011).

45 McClung M, Boonen S, Törring O *et al*. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. *J. Bone Miner. Res.* 27(1), 211–218 (2011).

46 Boonen S, Adachi JD, Man Z *et al*. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. *J. Clin. Endocrinol. Metab.* 96(6), 1727–1736 (2011).

47 Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr. Rev.* 23(4), 570–578 (2002).

48 Bone HG, Bolognese MA, Yuen CK *et al*. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J. Clin. Endocrinol. Metab.* 96(4), 972–980 (2011).

49 Fenwick E, Claxton K, Sculpher M. The value of implementation and the value of information: combined and uneven development. *Med. Decis. Making* 28(1), 21–32 (2008).

50 Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. *JAMA* 287(21), 2809–2812 (2002).

51 Fleurence RL, Spackman DE, Hollenbeak C. Does the funding source influence the results in economic evaluations? A case study in bisphosphonates for the treatment of osteoporosis. *Pharmacoeconomics* 28(4), 295–306 (2010).