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Original article

The cost effectiveness of zoledronic acid 5 mg for the management of postmenopausal osteoporosis in women with prior fractures: evidence from Finland, Norway and the Netherlands

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2739181; nbrereton@bresmed.co.uk**Key words:**Zoledronic acid 5 mg – Bisphosphonates –
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Citation: J Med Econ 2011; 14:53–64**Abstract****Objective:**

This study was conducted to assess the cost effectiveness of zoledronic acid 5 mg as a first-line treatment for the secondary prevention of fragility fractures in women with postmenopausal osteoporosis in Finland, Norway and the Netherlands.

Methods:A discrete-event, individual-patient computer-simulation model was used to compare the cost effectiveness of zoledronic acid with that of basic treatment (calcium and vitamin D) and commonly prescribed bisphosphonates in postmenopausal women aged 50–80 years who have experienced one previous fracture and have a bone mineral density T-score of -2.5 .**Results:**

The cost per quality-adjusted life-year (QALY) gained with zoledronic acid compared with basic treatment ranged from being cost saving in all age groups in Norway, to costing approximately €19,000 in Finland and €22,300 in the Netherlands. Compared with the other branded bisphosphonates, zoledronic acid was cost saving in many scenarios, including all age groups in Finland. In Norway, zoledronic acid dominated branded risedronate and ibandronate in all age groups and dominated or had incremental cost-effectiveness ratios (ICERs) of up to NOK83,954 per QALY gained compared with branded alendronate. In the Netherlands, zoledronic acid dominated branded intravenous ibandronate in all age groups; compared with branded risedronate and oral ibandronate, zoledronic acid dominated or had ICERs of up to €4832 per QALY gained; compared with branded alendronate, it had ICERs of up to €48,383 per QALY gained. In all three countries, zoledronic acid may be cost effective compared with generic alendronate when patient compliance with drug therapy is taken into account. Sensitivity analyses showed that the model was robust to changes in key values. The main model limitations were the lack of real-life compliance and persistence data, and lack of country-specific data for some parameters.

Conclusions:

Using local or commonly used thresholds, this analysis suggests that zoledronic acid would be a cost-effective first-line option compared with other branded bisphosphonates and, in some scenarios, compared with generic alendronate, for the secondary prevention of fractures in women with postmenopausal osteoporosis in Finland, Norway and the Netherlands.

Introduction

Postmenopausal osteoporosis is a major public health concern, incurring substantial healthcare costs. Osteoporosis is associated with significant morbidity and all-cause mortality following fragility fractures, particularly in the spine and hip. Such fractures lead to considerable disability, pain, hospitalisation, long-term care requirement, diminished quality of life, and an increase in all-cause mortality (particularly associated with hip fractures)^{1–3}. Patients who have experienced a fragility fracture are at increased risk for subsequent fractures^{4,5} and require effective, well-tolerated treatment. In Europe it has been estimated that 2.7 million osteoporotic fractures occurred in women aged ≥ 50 years in 2000; of these, over 711,000 were hip fractures⁶. Within Europe, Norway has one of the highest risks of hip fracture, while the Netherlands and Finland are described as 'high-risk' countries for osteoporotic fractures⁷. The direct costs incurred by osteoporotic fractures in Europe were estimated to be €27.5 billion in 2000⁶. The risk of osteoporotic fractures increases with age⁸ and the humanistic and economic burden will continue to escalate as the mean age of the population increases. Costs associated with osteoporotic fractures in European countries are estimated to rise to €36 billion by 2020 and to €54 billion by 2050⁶.

While currently available oral bisphosphonates and other antiresorptive agents are effective in treating osteoporosis, their effectiveness is compromised by poor compliance and persistence; for example, about 50% of patients fail to adhere to osteoporosis treatments by the end of the first year⁹. This has far-reaching consequences for patients' health and healthcare resource use. Several studies have demonstrated an association between poor compliance or persistence and an increased probability of fracture^{10,11}, with one study demonstrating that 50% compliance with oral bisphosphonate therapy gives only negligible fracture protection¹¹. Compliance and persistence with osteoporosis therapy thus also influence the costs associated with osteoporosis; poor compliance can result in wasted expense on drugs and increased costs due to fractures that could have been avoided^{10,12,13}.

Zoledronic acid 5 mg is highly effective in preventing fractures in women with postmenopausal osteoporosis¹⁴. Zoledronic acid 5 mg is unique among currently available osteoporosis treatments because it is administered as a once-yearly 15-minute intravenous infusion. This offers guaranteed 1-year treatment compliance and could potentially improve convenience to the patient through avoidance of the administration hurdles associated with oral bisphosphonate treatment, such as remaining in an upright position and food and drink restrictions. In addition, because administration of zoledronic acid 5 mg circumvents the gastrointestinal tract, it avoids the upper

gastrointestinal side-effects that are typical of oral bisphosphonates and which can lead to decreased treatment adherence¹⁵. Long-term patient persistence with zoledronic acid 5 mg treatment is therefore likely to be improved compared with the oral bisphosphonates.

The current study aimed to compare the cost effectiveness of once-yearly zoledronic acid 5 mg for first-line use in the secondary prevention of fragility fractures in women with postmenopausal osteoporosis against that of the most widely used osteoporosis drugs approved for this indication in Finland, Norway and the Netherlands at the time when zoledronic acid was introduced and/or reimbursement sought in these countries. Cost effectiveness was assessed to assist decision-makers in reimbursement and pricing decisions relative to other available treatments. The cost-effectiveness model used in the present study is based on the health technology assessments performed for the UK's National Institute for Health and Clinical Excellence (NICE) regarding the prevention and treatment of postmenopausal osteoporosis in the UK and published by Stevenson and colleagues^{8,16}. The model has been locally adapted for each country included in this analysis.

Methods

Study type

This cost-effectiveness analysis was conducted from the healthcare perspective of the countries studied, where healthcare comprises both community and institutionalised care. As in the approach taken by NICE and local guidelines, the analysis included those costs directly attributable to postmenopausal osteoporosis, but not indirect or intangible costs. Benefits were measured as quality-adjusted life-years (QALYs).

The cost-effectiveness model

Model structure

The analysis required the development of a discrete-event individual-patient computer simulation based on the model inputs used in the health technology assessments performed for NICE in the UK^{8,16}. However, while the time horizon of the model used for those assessments was limited to 10 years, the present model can accommodate the lifetime of each patient by using the SIMUL8[®] interface (SIMUL8[®] version 13.0; SIMUL8[®] Corporation, Boston, MA, USA). Each patient's path was tracked through the various transition states of the model, recording associated costs, all-cause mortality rates and health state utility values incurred as a result of fracture events (Figure 1). Each run of the model comprised

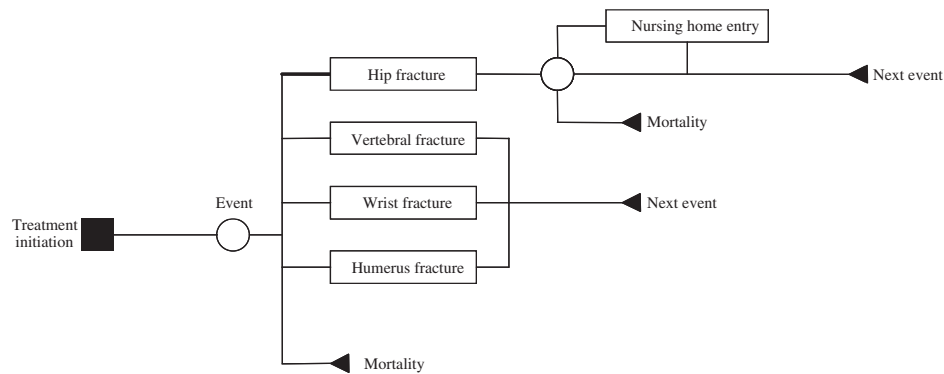


Figure 1. Structural diagram of the cost-effectiveness model.

100,000–250,000 patients, depending on the age group. A mean estimate was taken for the costs and QALYs of each modelled cohort.

As in the NICE model and other previous cost-effectiveness analyses of bisphosphonate therapy^{8,17,18}, it was assumed that patients were treated for 5 years, that the effect of treatment was instantaneous, and that the relative risk of fracture returned to 1 in a linear manner over a 5-year period following cessation of treatment. Thus, the treatment effect for each intervention was modelled for a total of 10 years. The model ran for the lifetime of each patient to fully capture the costs and consequences of fractures experienced during the treatment period.

Seven different events could occur in the model: hip, vertebral, humerus or wrist fractures, nursing home placement due to hip fracture, death due to hip fracture and death from any cause. On entry into the model, the patient's time of death was sampled from survival curves. With the exception of hip fracture, it was assumed that osteoporotic fractures do not affect all-cause mortality and so time of death was not re-sampled after a fracture event. The time to occurrence of the patient's first fracture event was sampled next. If the sampled fracture event occurred before the time of death, costs incurred and QALYs gained in the period up to the event and the cost and utility losses caused by the event were calculated. If the patient was still alive after the event, then the time to his or her next event was sampled, with the risk of the event modified by factors from the previous event, where appropriate. The process was continued until all patients in the model had their treatment history generated until their death.

The probability of incurring a fracture is dependent on the patient's absolute risk of a fracture given their age and their bone mineral density (BMD) T-score, their experience of previous fractures, and the effect of intervention. The time to fracture for each site was sampled by

calculating the annual probability of fracture. The annual risk of a fracture was calculated for each site as a hazard where:

Fracture hazard

$$= \text{Age/T-score-related fracture risk for untreated women} \\ \times \text{Intervention relative risk} \\ \times \text{Previous-fracture multiplier}$$

The probability of fracture was then calculated as $1 - \exp(-\text{fracture hazard})$

The efficacy outcome measure used was QALYs. The effect of baseline comorbidities was not included in the model. It was assumed that when a patient experienced a fracture at the same site for a second or subsequent time, only the initial year's reduction in quality of life would be taken into consideration; any long-term effects from previous fractures would be superseded.

Patient demographics

The analyses were run for a secondary prevention cohort, i.e. patients entering the model were assumed to have had one previous fracture. Patients were also assumed to have a BMD T-score of -2.5 and to be naïve to active osteoporosis treatment. Using sufficiently large numbers of patients to ensure stable results, the analyses were conducted for cohorts of postmenopausal women aged 50, 60, 70 and 80 years at the start of treatment.

Base-case analyses

The base-case scenario was run for branded zoledronic acid 5 mg once-yearly infusion [Aclasta®] and each comparator treatment (branded alendronate 70 mg oral once weekly [Fosamax®]; generic alendronate 70 mg oral once weekly; branded risendronate 35 mg oral once weekly [Actonel®/Optinate®]; branded ibandronate 150 mg oral once monthly and 3 mg injection once quarterly [Bonviva®])

against 'basic' treatment (placebo, calcium plus vitamin D). The base-case scenario was also applied for zoledronic acid 5 mg against each comparator treatment. For all analyses, costs incurred and the QALYs gained for each treatment were used to calculate the incremental costs per QALY gained. The incremental cost-effectiveness ratio (ICER) was defined as:

$$\frac{(C_1 - C_2)}{(Q_1 - Q_2)}$$

where C_1 and C_2 are the costs incurred when patients are treated with the specified bisphosphonate and basic treatment, respectively, and Q_1 and Q_2 are the QALYs gained through these treatments, respectively; or where C_1 and C_2 are the costs incurred when patients are treated with zoledronic acid 5 mg and one of the other specified bisphosphonates, respectively, and Q_1 and Q_2 are the QALYs gained through these treatments, respectively.

Sensitivity analyses

Sensitivity analyses were performed comparing zoledronic acid against branded alendronate. These included varying the drug costs; reducing the period during which nursing home costs are assumed to relate to the fracture causing nursing home entry; assessing patients with a lower T-score; and applying a 50% reduction in the cost of alendronate. A probabilistic sensitivity analysis was carried out using the Monte Carlo method to perform 1,000 runs of the model sampling from the distributions for all variables around which there was uncertainty. Sensitivity analyses were presented for the cohort of patients aged 70 years. A scenario analysis was performed to assess the impact on cost effectiveness of different levels of compliance with generic alendronate (the key comparator across all three countries), based on real-life data. Reduced compliance was applied in the model as diminished treatment effectiveness, which was extrapolated from the relationship described by Siris and colleagues for bisphosphonate efficacy in preventing fragility fractures¹¹. Hence 90% compliance resulted in an estimated 70% efficacy and 80% compliance resulted in an estimated 50% efficacy.

Parameter estimates and sources

Baseline risk of fracture

The current model incorporated estimates of patients' absolute risk of fracture, based on their age and T-score, and estimates of the distribution of previous fractures by age. For Finland and the Netherlands, epidemiological data on hip, wrist and proximal humerus fractures in women were derived from a large-scale Scottish study¹⁹ and data on vertebral fracture were taken from a study in Sweden²⁰, as used by Stevenson and colleagues⁸.

For Norway, local data were obtained for hip and wrist fractures^{21,22}, while data for humerus and vertebral fractures were taken from the Swedish study²⁰. General population fracture risks were adjusted to age and T-score specific risk as described in the analysis conducted for NICE⁸.

Events

Having an initial osteoporotic fracture greatly increases the risk for any subsequent osteoporotic fractures^{4,5} and this was taken into account in the model by applying previous-fracture multipliers to the risk values for the different fracture types. Previous-fracture multipliers obtained from Klotzbuecher and co-workers⁵ were adjusted downwards by 10% to adjust for BMD, as previously discussed^{4,8}. For individuals who had fractures at two or more different sites, only the greatest risk adjustment was applied when calculating the risk of subsequent fractures.

Estimates of the probability of nursing home entry due to hip fracture for the Norwegian population were: 6.0%, 8.5%, 25.6% and 33.1% for ages 50–69, 70–79, 80–90 and >90 years, respectively²³. For the Dutch population, the corresponding probabilities were 0%, 4%, 12% and 17%, respectively¹⁶. A probability of 12.5% was used for all age groups in the Finnish population²⁴.

All-cause mortality data for the different age groups were taken from local statistics^{25–27}. Weibull curves were fitted to the all-cause mortality data, which were then used to sample patients' time to death. As recently reviewed by Abrahamsen and colleagues³, excess all-cause mortality after hip fracture is well documented, hence after a patient experienced a hip fracture in the model they were probabilistically tested for mortality. Data for 1-year excess mortality subsequent to a hip fracture in patients in the community and in nursing homes were as used in the NICE analysis⁸.

Effectiveness

The reductions in the risk of fracture at each fracture site achieved with once-yearly zoledronic acid 5 mg treatment versus basic treatment were obtained from the results of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT) (Table 1)^{14,28}. This 3-year double-blind, randomised study assessed the efficacy and safety of zoledronic acid 5 mg compared with that of placebo in preventing fractures in 7736 women aged 65–89 years who had osteoporosis. All women also received calcium and vitamin D and the study was stratified to allow participants to take, in addition to study treatment, certain other approved treatments for osteoporosis, managed by their own physician.

No data were available from direct comparisons of bisphosphonates in women with postmenopausal

Table 1. Efficacy values for the prevention of fragility fractures in postmenopausal women.

Intervention	Mean relative risk of fracture event (95% CI)			
	Hip	Vertebra	Wrist	Proximal humerus
Zoledronic acid 5 mg ^{14,28}	0.59 (0.42–0.83)	0.30 (0.24–0.38)	0.81 (0.62–1.06)	0.58 (0.39–0.85)
Alendronate ^{8,29}	0.62 (0.40–0.98)	0.56 (0.46–0.68)	0.67 (0.34–1.31)	0.81 (0.68–0.97)
Risedronate ^{8,29}	0.74 (0.59–0.93)	0.61 (0.50–0.75)	0.68 (0.43–1.08)	0.76 (0.64–0.91)
Ibandronate ^{30–32}	1.00 (N/A)	0.38 (0.25–0.59)	1.00 (N/A)	1.00 (N/A)

CI, confidence interval; N/A, not applicable.

Table 2. Annual direct costs for patients with osteoporosis.

Costs	Finland (€)	Norway (NOK)	The Netherlands (€)
Fracture-associated costs ^a			
Hip fracture	8439 ³³	119,792 ^{b34}	15,912 ³⁵
Nursing home entry	43,971 impact cost; 41,172 annual cost ³³	577,706 ^{b36,37}	48,209 impact cost; 32,297 annual cost ^{35,38}
Death	8439 ³³	95,833 ^d	15,912 ³⁵
Vertebra	1070 impact cost ³³ ; 353 annual cost ³⁹	20,672 ^{b40}	7722 ³⁵
Proximal humerus	1010 (aged 50–80 years) 1757 (aged >80 years) ³³	16,958 ^e	3159 ³⁵
Wrist	918 (aged 50–80 years) 2012 (aged >80 years) ³³	16,958 ³⁴	1065 ³⁵
Drug costs ^{f,g}			
Zoledronic acid 5 mg ^h	529.73 ³⁹	3632.80 ⁴¹	428.92 ⁱ⁴²
Generic alendronate	367.30 ³⁹	663.52 ⁴¹	18.50 ⁴²
Branded alendronate	546.77 ³⁹	2765.70 ⁴¹	214.24 ⁴²
Risedronate	458.68 ³⁹	3115.40 ⁴¹	361.27 ⁴²
Ibandronate (oral)	546.00 ³⁹	3266.90 ⁴¹	353.28 ⁴²
Ibandronate (IV) ^h	1106.86 ³⁹	4686.40 ⁴¹	891.80 ⁴²
Other costs ^a			
Clinic visits	— ^g	260 ⁴³	— ^j

^aThe same costs were assumed for all ages unless otherwise stated; costs were for 2006 for Finland and the Netherlands and 2007 for Norway (relevant exchange rate: NOK1 = €0.125). ^bAdjusted from source for inflation and exchange rates. ^cYearly nursing home cost (NOK634,370) corrected for normal living costs for the elderly (NOK56,664). ^dAssuming 80% of cost of hip fracture. ^eAssumed to be the same as wrist fracture. ^f2008 costs (relevant exchange rate: NOK1 = €0.122).

^gFor Finland, drug costs include one clinic visit per year for oral bisphosphonates, one visit (including infusion) for zoledronic acid 5 mg and four visits (including the costs of injection) for IV ibandronate; costs of clinic visits taken from Hujanen³³. ^hIncludes cost for infusion, with the exception of IV ibandronate in the Netherlands.

ⁱInfusion costs from the Institute for Medical Technology Assessment, the Netherlands; personal communication. ^jCosts of visits not included. IV, intravenous.

osteoporosis. Data on the relative risk reductions (versus placebo) achieved with risedronate and alendronate (Table 1) were taken from the report by Stevenson and colleagues⁸ and the NICE Final Appraisal Determination on the secondary prevention of postmenopausal osteoporosis²⁹. Data for ibandronate were obtained from the package insert and published data (Table 1). It was assumed that oral and intravenous ibandronate have equivalent efficacy^{30–32}. Ibandronate does not have proven antifracture efficacy at non-vertebral sites, so the relative fracture-risk reduction for these sites was 1.0.

It was assumed that the treatment effect observed in clinical trials was independent of patients' baseline risk factors, i.e. age and T-score.

Costs

Only costs directly attributable to a fracture event and its direct treatment and follow-up were included in the analyses (Table 2), with local costs being used where available.

Where local costs were not available, source costs were adjusted for inflation and exchange rates applied. Costs for BMD scans were not included in the analyses as it was assumed that scans would be performed before the point in the patients' management at which the model starts. It was assumed that all patients received adequate calcium and vitamin D; costs for supplements were not included in the model. All costs are presented in the local currency and were annually discounted (to convert future costs to present values) at the locally acceptable rates: 5.0% for Finland^{44*}; 4.0% for Norway (Norwegian Medicines Agency, personal communication); and 4.0% for the Netherlands⁴⁶.

It was assumed that patients entering a nursing home because of hip fracture would remain there for the rest of their lives. Costs comprised the initial impact cost and then an annual cost associated with the nursing home stay.

*This was the rate applicable at the time of the analysis. The most recent guidance (2009) recommends a rate of 3.0%⁴⁵.

Annual costs of osteoporosis interventions included the costs of infusion for zoledronic acid 5 mg in all countries and for intravenous ibandronate in Finland and Norway (Table 2). Costs for visits were also included. It was assumed that after the treatment period, no further costs were incurred for interventions.

For the sensitivity analysis of the impact of reduced compliance on cost effectiveness, annual drug acquisition costs were decreased in proportion to the amount of drug not obtained by the patient.

Quality of life

On entering the model the patient with osteoporosis was considered to be healthy, i.e. not experiencing any adverse effects due to hip, vertebral or wrist fracture. This baseline health state was assigned an age-specific utility value based on those for the UK general population: 0.850, 0.829, 0.747 and 0.699 at ages 50, 60, 70 and 80 years, respectively⁸. On experiencing a fracture, the patient was assigned a utility value for the first year of the event, as described by Stevenson and colleagues¹⁶. This was calculated by applying a fracture-specific utility multiplier, which proportionally reduces the patient's utility for the year^{47,48}. The multipliers for hip, proximal humerus, vertebral and wrist fracture, and for hip fracture leading to nursing home entry were 0.792, 0.794, 0.626, 0.977 and 0.400, respectively^{47,48}. It was also assumed that for some fractures the patient could not recover in subsequent years to the level of health experienced before the event. Each fracture type was thus assigned a utility 'ceiling' multiplier to represent the maximum level of health to which patients could recover (0.813, 0.973, 0.909, 0.999 and 0.400, respectively)^{16,47,48}. The multipliers were applied to the baseline utility value to give the ongoing proportional disutility caused by the fracture. QALYs were annually discounted according to local guidance at the following rates: 5.0% for Finland⁴⁴; 4.0% for Norway (Norwegian Medicines Agency, personal communication); 1.5% for the Netherlands⁴⁶.

Results

The internal validity of the model was demonstrated as the number of fractures predicted by the model was consistent with that observed in the epidemiology data. The results are presented from the healthcare perspective of each of the three countries, where healthcare includes residential care following a fracture.

Base-case analyses

The results of the base-case analyses are shown in Figures 2 and 3. For all three countries, compared with basic

treatment (calcium and vitamin D), the cost per QALY gained (ICER) in any age group was highest for ibandronate and lowest for generic alendronate (Figure 2). In Finland, zoledronic acid 5 mg had a lower ICER than all other branded bisphosphonates, with the cost per QALY gained decreasing from approximately €19,000 for a woman aged 50 years to €8300 for a woman aged 80 years (Figure 2a). In Norway, zoledronic acid 5 mg, riseridronate and alendronate (branded and generic) dominated over basic treatment, with the ICER dropping substantially between the ages of 70 and 80 years (Figure 2b). Compared with basic treatment, zoledronic acid 5 mg had lower ICERs than branded riseridronate and ibandronate. In the Netherlands, compared with basic treatment, zoledronic acid 5 mg had lower ICERs than branded riseridronate and ibandronate and ranged from being cost-saving in women aged 80 years to having a cost per

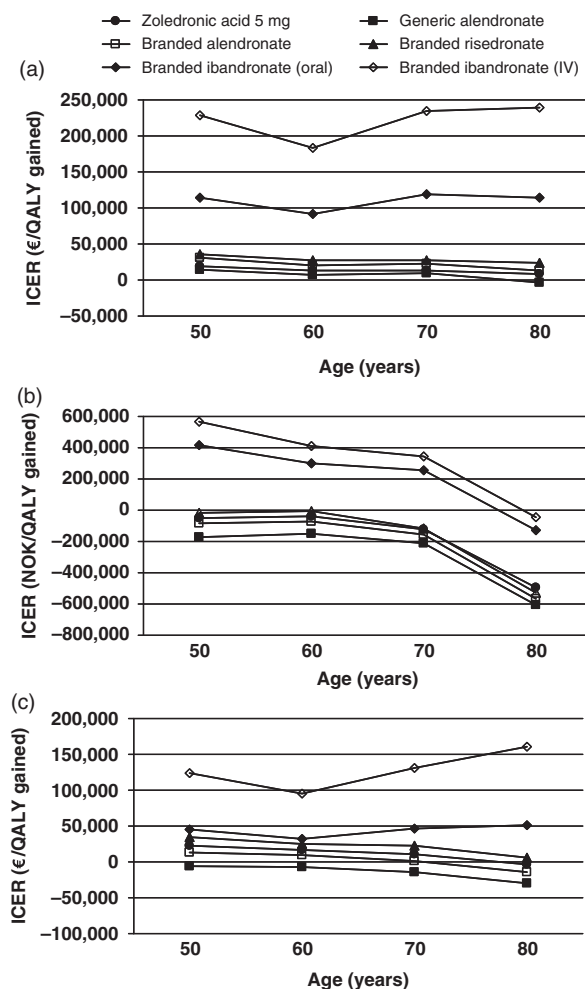


Figure 2. Cost effectiveness by age group for selected bisphosphonates compared with basic treatment in (a) Finland, (b) Norway and (c) the Netherlands. Negative values indicate dominance, i.e. better efficacy and lower cost. ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life-year.

QALY gained of €22,330 (Figure 2c). Generic alendronate dominated over basic treatment at all ages.

Zoledronic acid 5 mg was also a favourable option when ICERs were calculated directly in comparison with other bisphosphonates. In Finland, zoledronic acid 5 mg

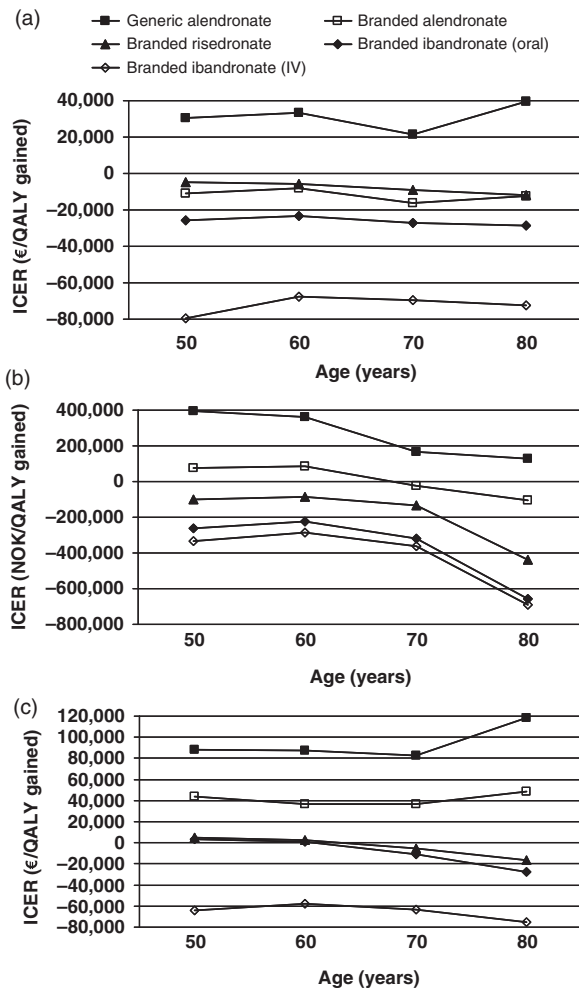


Figure 3. Cost effectiveness by age group for zoledronic acid 5 mg compared with selected bisphosphonates in (a) Finland, (b) Norway and (c) the Netherlands. Negative values indicate dominance, i.e. better efficacy and lower cost. ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life-year.

dominated over all the branded options for all age groups (Figure 3a). Compared with generic alendronate, the ICERs ranged from €21,419 to €39,614 per QALY gained (patients aged 70 and 80 years, respectively). Similarly, in Norway, zoledronic acid 5 mg dominated over branded ibandronate (oral and intravenous) and branded risedronate (Figure 3b). Zoledronic acid 5 mg dominated branded alendronate in patients aged 70 and 80 years; in patients aged 50 and 60 years, the ICER for zoledronic acid 5 mg compared with branded alendronate was NOK76,188 and NOK83,954 per QALY gained, respectively. Compared with generic alendronate, the ICERs for zoledronic acid 5 mg ranged from NOK130,794 to NOK396,574 per QALY gained (patients aged 80 and 50 years, respectively). In the Netherlands, zoledronic acid 5 mg dominated branded intravenous ibandronate at all ages and dominated branded oral ibandronate and risedronate in patients aged 70 and 80 years (Figure 3c). In patients aged 50 and 60 years, the ICERs for zoledronic acid 5 mg compared with branded oral ibandronate were €3124 and €923 per QALY gained, respectively; compared with branded risedronate the ICERs were €4832 and €2394, respectively. Compared with branded alendronate, the ICERs for zoledronic acid 5 mg ranged from €36,927 per QALY gained in patients aged 60 years to €48,383 per QALY gained in those aged 80 years. The ICER profiles were notably different between the countries, with ICERs remaining fairly similar across the age groups for Finland and the Netherlands, but decreasing after age 60 years and again after age 70 years in Norway.

Sensitivity analyses

Results of sensitivity analyses show that the model was robust to changes in key values and assumptions (Table 3). Application of lower values for compliance with generic alendronate – and hence decreased drug effectiveness – caused a substantial lowering in the ICERs for zoledronic acid 5 mg versus generic alendronate across all age groups in all countries (Table 4).

Table 3. Sensitivity analyses: Incremental cost-effectiveness ratios for zoledronic acid 5 mg versus branded alendronate.

Scenario	Finland (€)	Norway (NOK)	The Netherlands (€)
Base case	25,287	Dominant	873
Reducing cost of alendronate by 50%	52,746	15,789	20,157
Restricting nursing home costs to 3 years	26,997	Dominant	1887
Patients with a lower T-score (–3.5)	22,734	Dominant	Dominant
50% reduction in long-term utility decrement for hip and vertebral fractures	28,063	Dominant	1477
PSA results*	57%	87%	79%

*Probability that cost effective at a threshold of €30,000 or NOK200,000.
PSA, probabilistic sensitivity analysis.

Table 4. Sensitivity analyses: Incremental cost-effectiveness ratios for zoledronic acid 5 mg versus generic alendronate at different compliance rates for generic alendronate.

Age (years)	Compliance with generic alendronate		
	100%	90%*	80%*
Finland (€)			
50	30,258	11,216	4450
60	33,527	12,523	6756
70	21,419	6774	669
80	39,614	9709	2529
Norway (NOK)			
50	396,574	126,744	10,179
60	363,009	50,511	12,286
70	166,726	-8370	-69,670
80	130,794	-281,242	-354,558
The Netherlands (€)			
50	88,102	50,698	36,098
60	87,092	42,966	30,414
70	82,327	36,919	25,248
80	118,800	39,035	16,519

*A 90% level of patient compliance was calculated to give 70% of maximal drug efficacy in preventing fracture and 80% compliance to give 50% efficacy, as described by Siris *et al.*¹¹.

Negative values indicate that zoledronic acid 5 mg was dominant, i.e. more effective, at a lower cost.

Discussion

The present study assessed the cost effectiveness of zoledronic acid 5 mg and key comparator drugs as first-line therapy for secondary prevention of fractures in postmenopausal women with one previous fracture and a T-score of -2.5 in Finland, Norway and the Netherlands at the time when zoledronic acid was introduced and/or reimbursement sought in these countries. A particular strength of this study was the model used; the discrete-event individual-patient model using SIMUL8[®] software has a distinct advantage over the cohort models used in some previous analyses in that it avoids the need for a large number of health states in order to correctly apply combinations of factors such as prior fractures and residential status. Such factors are more accurately employed in the individual-patient model where a full patient history is created. In addition, the current model has advantages over the model used in the assessments conducted for NICE^{8,16}. Although the NICE model also considered individual patient data, it was not based on discrete-event simulation; furthermore it was developed using Microsoft Excel software, which has restrictive processing and therefore required a Gaussian approximation to improve processing speed. It was thus limited in its time horizon and adaptability, compromising the accuracy of the results and the ability to vary assumptions. In contrast, by employing SIMUL8[®], the model used in the present study allows simulation of events throughout the individual patient's lifetime.

The comparator drugs chosen for analysis are those most commonly prescribed for osteoporosis in the

countries studied. Generic alendronate has generally become the most frequently prescribed bisphosphonate. The analyses were conducted from what is termed a 'healthcare perspective', however, the authors recognise that in reality the cost of care for institutionalised patients might be funded from a different source to the other costs.

At present, no formally recognised thresholds for cost effectiveness (cost per QALY gained) are available in the countries studied. For the Netherlands, an often quoted willingness-to-pay threshold stems from the guideline on cholesterol-lowering drugs issued in 1998, which mentions a value of €18,000 per QALY gained⁴⁹. However, in 2006, the Dutch Council for Public Health and Health Care stated that it might be acceptable to pay €80,000 per QALY gained for indications with a very high disease burden and unmet need⁵⁰. For Finland and Norway, it was assumed that the threshold applied by NICE in the UK would be applicable for the purposes of the current study, i.e. approximately £20,000–£30,000 per QALY gained. Using these thresholds (€80,000 for the Netherlands, €30,000 for Finland and Norway), zoledronic acid 5 mg was either dominant or cost effective compared with basic treatment in women with postmenopausal osteoporosis (T-score -2.5 , one previous fracture) aged 50–80 years in all three countries. Zoledronic acid 5 mg was also dominant or cost effective compared with the other branded bisphosphonates most commonly prescribed for postmenopausal osteoporosis in the three countries examined, at all ages tested. Compared with generic alendronate, at the lower levels of compliance assessed, zoledronic acid 5 mg would probably be cost effective or even dominant in all age groups tested for all three countries. Even assuming full patient compliance with the oral bisphosphonate, zoledronic acid 5 mg was a cost-effective alternative for patients aged 70 years in Finland and for patients aged 70–80 years in Norway.

The differences in results observed between the countries included in the analysis are primarily driven by the differences in baseline risk of fracture and its incidence, annual cost of treating fractures and drug acquisition costs. In particular there is a much higher risk of hip fracture in the Norwegian epidemiology data compared with Finland and the Netherlands; due to the high cost of treatment, this is a key driver of the cost effectiveness. Other country-specific variations in the modelled data are likely to have contributed to these differences; for example, in the Finnish analysis, increased costs were applied to patients aged >80 years in association with some types of fractures. It is also noticeable that the ICERs change more dramatically with age in some scenarios than in others. For example, in Norway the ICERs for all bisphosphonates versus basic treatment decrease substantially at age 80 years compared with other age groups, and in Finland the ICERs for zoledronic acid 5 mg versus generic alendronate are much lower in patients aged 70 years than for other age groups.

In addition to differences in local costs, such changes may in part be due to an increased proportion of fractures in these age groups being hip fractures – the most costly type of fragility fracture to manage. For example, in Norway the risk of hip fracture and the probability of subsequent nursing-home entry was higher in older age groups (>75 years) compared with the other countries.

The costs included in the study are those applicable in 2008 when zoledronic acid 5 mg entered the market. Since these analyses were conducted, drug prices have changed and a greater number of generic alendronate formulations as well as generic risedronates have become available in some countries. In the specified scenarios – and when compliance is taken into account – the principal outcomes of the present analyses are likely to prevail: that zoledronic acid 5 mg is likely to be a cost-effective option compared with other branded bisphosphonates and may be cost effective compared with generic formulations. However, given the recent rapid changes in drug costs and availability in this therapeutic area, any future assessments of the relative cost effectiveness of these drugs should incorporate current local costs and formularies.

The model was used as originally populated for reimbursement applications. The data incorporated in the model were obtained from local sources and from data previously used in the analyses conducted for NICE in the UK⁸. For Finland and the Netherlands some of the epidemiological data (hip, wrist and proximal humerus fracture rates) were taken from a Scottish study used in the NICE analysis, rather than from local sources. Fracture incidence in Finland and the Netherlands is very similar to that in the UK⁵¹, however, the authors acknowledge that local differences in fracture incidence rates, particularly for hip fracture, may affect the cost-effectiveness outcomes. The authors are also aware that studies that could provide data have been conducted since the present model was constructed⁵². Assumptions were also made regarding some of the efficacy data for comparator agents. To date, ibandronate has not been shown in randomised clinical trials to have antifracture efficacy at non-vertebral sites³², so for the purposes of the model, a relative risk reduction of 1.0 was assigned at these sites. Recent analyses of pooled data have suggested that higher doses of ibandronate may reduce non-vertebral fracture risk in postmenopausal women^{53,54}, but this remains to be proven in a clinical trial.

The current analysis modelled a particular set of scenarios in which a number of factors were included, however, it was not possible to encompass all possible influences on cost and efficacy. Some of the factors that may alter cost effectiveness in clinical practice are discussed below and demonstrate that the data presented – and hence the cost-effectiveness results – are likely to be conservative estimates, in particular for zoledronic acid 5 mg.

The present study considered patients with a T-score of -2.5 , the minimum threshold for osteoporosis. Although a low T-score is not the only indicator of risk, and several other factors should be taken into account in clinical practice, patients with lower T-scores are at greater risk of fracture. Treatment with a bisphosphonate would thus be expected to avoid more fractures and be even more cost-effective than basic treatment in such patients compared with those at the minimum threshold of osteoporosis.

When applying fracture-associated reductions in quality of life, it was assumed that the impact of the fracture with the most severe utility detriment superseded any effect of previous or current fracture(s), thus in the model it is possible to have a fracture that has no utility impact (for example a wrist fracture following a hip fracture). Such conservative assumptions contribute to an underestimation of the cost effectiveness of treatments with better fracture prevention.

One of the most important aspects of osteoporosis treatment is adherence to therapy. As for many drugs used to treat predominantly asymptomatic conditions, compliance and persistence with osteoporosis medications are poor. Studies of real-world patient activity have revealed that up to 50% of patients have discontinued oral bisphosphonates by the end of the first year of treatment^{9,55}. Persistence and compliance diminish even further over longer periods; for example, van den Boogaard and colleagues showed that 2-year persistence with weekly bisphosphonates was as low as 26%⁵⁶. Several studies have demonstrated that poor compliance and/or persistence with bisphosphonates have a significant negative impact on treatment outcomes^{10,11}. Meijer and colleagues have also shown that continued compliant use of bisphosphonates is required to maintain efficacy in preventing fracture⁵⁷. Given that a minimum of 50% compliance is required in order to attain anything above negligible clinical efficacy¹¹, it is likely that many patients prescribed oral antiresorptives are not achieving optimal fracture protection. Not surprisingly, modelled analyses of bisphosphonate treatment for postmenopausal osteopenia or osteoporosis have shown that compliance and persistence have an effect on cost effectiveness^{58,59}. Although the genericisation of alendronate may reduce drug acquisition costs, recent data suggest that persistence with generic alendronate is even poorer than with branded alendronate⁶⁰.

The sensitivity analyses conducted in the present study investigated the potential impact on cost effectiveness of suboptimal compliance. Annual compliance rates of 90% and 80% for generic alendronate would result in zoledronic acid 5 mg being a cost effective or dominant option in many age groups. The compliance rates assumed in the sensitivity analyses are still very conservative compared with what might be expected in clinical practice, and it was also assumed that the level of compliance would be the

same for each of the 5 years of treatment. In reality, compliance and persistence with the comparators included in the present study are likely to be lower than assumed in the model and hence their cost-effectiveness values are likely to be lower than calculated. Persistence and compliance with zoledronic acid 5 mg was assumed to be 100% in both the base-case and sensitivity analyses. This can be confidently assumed for the first year of treatment, as a single infusion guarantees 1 year of exposure. Surveys of patient preference in clinical trials of zoledronic acid 5 mg versus weekly alternatives (while still blinded to treatment) show that patients predominantly prefer yearly administration and thus suggest that patients will be more likely to persist with such therapy^{61,62}. In the HORIZON-PFT approximately 80% of patients received all three scheduled infusions of zoledronic acid 5 mg¹⁴. However, persistence levels for zoledronic acid 5 mg in clinical practice are as yet unexplored, due to a lack of real-life usage data at the time this cost-effectiveness study was conducted; thus the sensitivity analyses could not incorporate the levels of compliance and persistence that might occur in real clinical practice. Despite this, the study has demonstrated the effect of the differences in compliance that might be reasonably expected between zoledronic acid 5 mg and generic alendronate. Further real-life analyses of compliance and persistence beyond the first infusion are planned once sufficient data have been collected for zoledronic acid 5 mg in women with postmenopausal osteoporosis.

Treatment-associated adverse events were not included in the model. In clinical practice, the oral bisphosphonates are likely to be associated with upper gastrointestinal adverse events that may require additional visits to a primary care physician and additional treatment. Such events may also lead to reduced quality of life and to discontinuation. With regard to zoledronic acid 5 mg, a low number of patients may experience post-dose flu-like symptoms. Clinical trials have shown these events to be generally mild to moderate and transient, usually resolving within 3 days and diminishing with each subsequent annual infusion¹⁴. The symptoms can be reduced by administering paracetamol (acetaminophen) or ibuprofen before the intravenous infusion⁶³ with a minimal impact on costs. Thus, given that the most common adverse events occurring with zoledronic acid 5 mg would have little impact on cost-effectiveness, while the costs and effects of gastrointestinal adverse events associated with oral bisphosphonates would diminish their cost effectiveness, the estimates reported in this study of zoledronic acid's cost effectiveness relative to the oral bisphosphonates are likely to be conservative.

The model assumed that all the drugs involved would affect all-cause mortality only to the degree that they prevent hip fracture. The HORIZON-Recurrent Fracture Trial (HORIZON-RFT) demonstrated that zoledronic

acid 5 mg was associated with a significant 28% reduction in the risk of all-cause mortality in patients who had experienced a hip fracture⁶⁴. To what extent this was due to the reduction in hip fracture in the study population is unknown, but there may be other factors involved that were not taken into account in the current model. As the HORIZON-RFT population was different to that modelled in the present study – the former comprised male and female patients, all with hip fracture and many with a T-score below –2.5 – the all-cause mortality benefit observed in this study was not applied in the model. There is also evidence that vertebral fractures are associated with an increased risk of all-cause mortality^{65–67}, although the risk has not been well characterised. However, given that the drugs included here – in particular zoledronic acid 5 mg – are effective in preventing vertebral fracture, they are likely to be more cost effective compared with basic treatment in clinical practice than estimated by the present analysis if all-cause mortality following vertebral fracture is considered. In addition, the current model used estimates of excess mortality occurring within 12 months after a hip fracture⁸. In reality, the impact of hip fracture on mortality is likely to be longer lasting, possibly up to several years³. Thus, the benefit derived from prevention of hip fracture may be more extensive than considered in the model, again suggesting that the present estimates of zoledronic acid's cost effectiveness may be conservative.

Conclusions

Zoledronic acid 5 mg represents an effective new treatment for osteoporosis in postmenopausal women. Compared with oral antiresorptive therapies, it has the potential advantage of extended effectiveness because the once-yearly infusion is sufficient to provide year-long exposure without the problems of poor compliance that are associated with oral agents.

Based on clinical trial efficacy data, the current study has shown that in postmenopausal women with osteoporosis requiring secondary prevention of fragility fractures (i.e. women with a previous fracture and a T-score of –2.5) in Finland, Norway and the Netherlands, the use of zoledronic acid 5 mg is likely to translate into a cost-effective first-line approach compared with basic treatment and with the most commonly prescribed branded bisphosphonates. In addition, in some scenarios, zoledronic acid 5 mg may be a cost-effective alternative to generic alendronate.

Transparency

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Declaration of financial/other relationships

R. Akehurst received payment from Novartis for the original model development to support reimbursement submissions relating to zoledronic acid but did not receive fees or funding in relation to the development of the current manuscript; he is also a paid adviser to Novartis on other products.

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