ORIGINAL ARTICLE

Cost-utility of long-term strontium ranelate treatment for postmenopausal osteoporotic women

M. Hiligsmann · O. Bruyère · J.-Y. Reginster

Abstract

Summary The results of this study suggested that long-term treatment with strontium ranelate over 5 years is cost-effective compared to no treatment for postmenopausal osteoporotic women.

Introduction This study aims to estimate the cost-effectiveness of long-term strontium ranelate treatment for postmenopausal osteoporotic women.

Methods A validated Markov microsimulation model with a Belgian healthcare cost perspective was used to assess the cost per quality-adjusted life-year (QALY) of strontium ranelate compared to no treatment, on a basis of calcium/vit D supplementation if needed. Analyses were performed for women aged 70, 75, and 80 years either with a bone mineral density T-score ≤ -2.5 SD or with prevalent vertebral fractures. The relative risk of fracture during therapy was derived from the Treatment of Peripheral Osteoporosis Study trial over 5 years of treatment. Parameter uncertainty was evaluated using both univariate and probabilistic sensitivity analyses.

Results Strontium ranelate was cost-saving at the age of 80 years in both populations. For women with a T-score ≤ -2.5 SD, the costs per QALY gained of strontium ranelate were respectively €15,096 and €6,913 at 70 and 75 years of age while these values were €23,426 and €9,698 for women with prevalent vertebral fractures. Sensitivity analyses showed that the results were robust over a wide range of assumptions.

Conclusion This study suggested that, compared to no treatment, long-term strontium ranelate treatment is cost-effective for postmenopausal osteoporotic women.

Introduction

Since two decades, several treatment options have been developed for the management of postmenopausal osteoporosis [1]. Oral bisphosphonates have demonstrated their ability to reduce vertebral and non-vertebral fractures. But, for daily and weekly formulations, their long-term efficacy, in real life settings, was jeopardized by a poor adherence to treatment. More recent treatment options include oral monthly or IV quarterly and yearly infusions of bisphosphonates [2, 3] as well as treatments characterized by a new mode of action. Strontium ranelate has shown, in preclinical studies, its ability to concomitantly reduce bone resorption and stimulate bone formation, hence, becoming the first agent of a new therapeutic class of uncoupling agents. In clinical trials, strontium ranelate has been shown to significantly reduce vertebral and non-vertebral fractures in a wide scatter of patients, from osteopenia to very elderly subjects, over a long-period of time (up to 5 years) [4–7]. In addition to the therapeutic value (e.g. safety, efficacy) of a drug, evidence of cost-effectiveness plays an increasingly role to assist health policy decision making [8]. Many countries have introduced formal guidelines or requirements for economic studies as part of the pricing or reimbursement decision [9].

M. Hiligsmann (✉) · O. Bruyère · J.-Y. Reginster
Department of Public Health, Epidemiology and Health
Economics, University of Liège,
Avenue de l'hôpital 3, Bat B23,
4000 Liège, Belgium
e-mail: m.hiligsmann@ulg.ac.be

M. Hiligsmann
Department of Economics, University of Liège,
Liège, Belgium

The aim of this study was to assess the cost-effectiveness of long-term strontium ranelate in the treatment of postmenopausal osteoporotic women. A validated Markov microsimulation model [10] was used to estimate the incremental cost-effectiveness ratio of strontium ranelate versus no treatment in a basis of calcium/vit D supplementation, if needed, using data from the Treatment Of Peripheral Osteoporosis Study (TROPOS) trial over 5 years of treatment [5]. Analyses were performed for women aged 70 years and older either with a bone mineral density (BMD) *T*-score≤−2.5 SD or with prevalent vertebral fractures, based on the two conditions for reimbursement of anti-osteoporotic therapy in Belgium, the country of reference for the present analysis.

Materials and methods

Economic model

A validated Markov microsimulation model [10] provides cost-utility analyses undertaken from a direct health care cost perspective, as recommended for pharmacoeconomic evaluations in Belgium [11]. The model consisted of six health states: no fracture, hip fracture, clinical vertebral fracture, forearm fracture, other fracture, and death. All the patients began in the state of no fracture and all the transitions between health states were possible, in each cycle and regardless of the current state. The patient history was recorded by so-called tracker variables and thus prior fractures and current residential status (either in the community or in a nursing home) were used in calculations of transition probabilities, quality-adjusted life-year (QALY), and costs. The cycle length is 1 year and the time horizon was patient lifetime. The required time horizon to fully evaluate the benefit of a particular intervention should be very long because fractures have long-term impact on quality of life and are associated with long-term costs. The use of a lifetime horizon has therefore been recommended for chronic diseases such as osteoporosis [12]. Each state has its associated costs and QALY, depending on the patient history. Fracture costs included direct costs and long-term costs beyond the first year after hip fracture for women in a nursing home. The disutility associated with fractures was modeled as a relative reduction in quality of life and an excess mortality was assumed after hip and clinical vertebral fractures. Costs (expressed in €2006) and health benefits were discounted at respectively 3% and 1.5% [11].

All the model parameters were selected from Belgian literature when available and from systematic literature review otherwise. Hip fracture risk and the cost of hip fracture were derived from Belgian epidemiological studies

[13–15]. Incidence of other fractures have been imputed using fracture rates from other countries, assuming that the ratio between hip and other fractures would be similar between countries. The costs of clinical vertebral and other fracture have also been quantified relative to hip fracture on the basis of their costs [16, 17]. The impact of osteoporotic fractures on quality of life was derived from a recent systematic review of the literature [18]. For a full description of the data and the model's assumptions, please refer to our paper published in Value in Health [10], which described and validated our model. The developed model was also used to estimate the effect of changes in baseline population risk and changes in life expectancy on absolute lifetime fracture risks [19].

Model populations

Analyses were assessed in two patients groups to match the population in Belgium for whom osteoporosis medications are currently reimbursed, i.e. women with a BMD *T*-score≤−2.5 SD or with prevalent vertebral fractures. Fracture risk needs to be adjusted to accurately reflect the fracture risk in these populations in comparison with that of the general population. In this way, the risk of first fracture in the general population [19] was adjusted by a relative risk.

For women with a BMD *T*-score≤−2.5 SD, the relative risk for all women below the threshold value for osteoporosis compared to the risk in the general population was calculated from the BMD, using a method previously described [20]. The number of standard deviations of BMD below the age-matched average BMD was derived from the recommended NHANES III [21] database and we assumed that one standard deviation decrease in BMD was associated with a relative risk of 1.8, 1.4, and 1.6, respectively for clinical vertebral, forearm, and other osteoporotic fracture [22]. The relative risk for hip fracture was shown to decrease with age and ranged from 3.68 (at 50 years) to 1.93 (at 85 years) [23]. All the relative risks per standard deviation decrease in BMD were calculated for women and men combined.

For women with prevalent vertebral fractures, the relative risks were taken from a meta-analysis and were respectively 2.3, 4.4, 1.4, and 1.8 for hip, clinical vertebral, wrist, and other osteoporotic fracture [24]. These relative risks were reduced by 10% per each decade above the age of 70 years [25]. We also assumed that further fractures during the simulation process had no additional effect on fracture risk.

Strontium ranelate

In order to assess the cost-effectiveness of strontium ranelate, data are required on fracture reduction efficacy

(at specific sites), on treatment dosage and duration, on the effect of treatment after stopping therapy, on adherence to therapy, and on treatment adverse events and costs.

The effect of strontium ranelate on fracture risk was taken from the 5-year results of the TROPOS study [5] (see Table 1). This study was a multinational randomized double-bind, placebo-controlled study, including 5,091 osteoporotic women above 70 years of age. Strontium ranelate, 2 g sachet once daily, was therefore assumed to reduce the risk of vertebral fracture by 24% (relative risk 0.76, 95% CI 0.65–0.88) compared with placebo and the risk of wrist and other fractures by 18% (relative risk 0.82, 95% CI 0.69–0.98) using the estimated fracture risk reduction for major non-vertebral fractures [5]. The effect of strontium ranelate on hip fracture was derived from the subset of patients analyzed for hip fracture (i.e. patients aged 74 years or older with a femoral neck BMD T-score≤ –2.4 SD according to NHANES reference [21]), which showed a significant fracture risk reduction at the hip (relative risk 0.57, 95% CI 0.33–0.97). Because the post hoc analysis was restricted to women aged 74 years and older, an additional scenario was performed for women aged 70 years, which assumed that strontium ranelate reduced the risk of hip fracture by only 18% using the estimated fracture risk reduction for major non-vertebral fractures.

Patients were assumed to receive strontium ranelate for 5 years, as in the clinical trial. The residual effect of therapy after discontinuation plays an important role in the cost-effectiveness of therapies [26, 27]. A recent study showed that patients who switched from strontium ranelate to placebo after 4-year treatment experienced a progressive reduction in BMD [28]. Slope of decrease in BMD observed 1 year after treatment cessation was similar to the slope of increase during the previous years of therapy. We therefore assumed a gradual linear loss of fracture reduction benefit over 5 years after treatment cessation.

Table 1 Relative risk of fracture at the sites shown for strontium ranelate and annual therapy cost

Parameters	Value
Relative risk of fracture during therapy	
Hip fracture	0.57 (95% CI 0.33–0.97) [5]
Hip fracture: additional scenario[a]	0.82 (95% CI 0.69–0.98) [5]
Vertebral fracture	0.76 (95% CI 0.65–0.88) [5]
Forearm fracture	0.82 (95% CI 0.69–0.98) [5]
Other fracture	0.82 (95% CI 0.69–0.98) [5]
Annual therapy cost	€ 512.56 [34]

CI confidence interval

[a] Only for women aged 70 years

This assumption has been frequently used in previous studies of the cost-effectiveness of anti-osteoporotic therapy [29, 30] and was tested in sensitivity analysis.

Adherence to anti-osteoporotic medications is currently low [31] and may affect the cost-effectiveness of treatments [10]. Adherence to strontium ranelate in general clinical practice has not yet been documented. We therefore assumed in the base-case analysis that all patients were fully adherent. In a sensitivity analysis, adherence to strontium ranelate was assumed to be similar to that observed for bisphosphonate therapy in Belgium [32]. Adherence is a general term and was investigated by two different constructs, i.e. compliance and persistence. Medication compliance may be defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" and medication persistence as "the duration of time from initiation to discontinuation of therapy" [33]. We assumed that 30%, 12%, 18%, and 15% of patients discontinued therapy after 3 months, 6 months, 1 year, and 2 years, respectively. No treatment effect was assumed for patients who discontinued treatment at 3 months and offset time for non-persistent patients was assumed to be the same as their treatment period. Compliance was estimated at 70.5% for persistent women [32]. Medication costs and fracture reduction efficacy were assumed to be proportional to compliance.

Units costs for medication were based on the official listings of the Belgian Center for Pharmacotherapeutic Information (2008) [34]. The annual cost of strontium ranelate was estimated at €512.6 (Protelos®, €117.96 for a package of 84 sachets). In accordance with previous standard assumptions regarding the monitoring of osteoporotic treatments [29], we also assigned the cost of one physician visit (€20) for each year of therapy and the cost of a BMD measurement (€47) every second year.

Adverse events observed with strontium ranelate are usually mild and transient [35]. More patients in the strontium ranelate group than in the placebo group reported nausea (7.8% versus 4.8%) and diarrhea (7.2% versus 5.45%) [5]. The incidence of venous thromboembolic events was also greater in the strontium group (i.e. 2.7% compared to 2.1% in the placebo group) but the differences between group were not statistically significant [5]. Therefore, the cost and quality of life impact of the adverse events will be minor and were not included. We also conservatively assumed no quality of life increase during therapy.

Sensitivity analyses

Uncertainty related to model parameters and assumptions was investigated using both univariate and probabilistic

sensitivity analyses. Univariate sensitivity analyses were conducted to assess the impact of single parameter variations on the results. The baseline parameters for discount rates, fracture risk, fracture disutility, fracture cost, and excess mortality were varied over plausible ranges. The cost-effectiveness of strontium ranelate for women at the threshold for osteoporosis (i.e. BMD T-score of –2.5 SD) and without a prior fracture was also estimated. Potential changes in therapy were also tested and included adherence, monitoring costs, therapy cost, efficacy, offset time, and effect on quality of life.

Probabilistic sensitivity analyses were also performed to analyze the effects of uncertainty in all model parameters simultaneously. Distributions used for key model inputs have been previously described and validated [10]. Log-normal distributions were also assumed for the relative fracture risks of strontium ranelate, as recommended by Briggs's book for relative risk parameters [36] and were derived from 95% confidence intervals [5]. The distributions of the relative fracture risks associated with BMD T-score≤−2.5 SD and with prevalent vertebral fractures were respectively assumed to be log-normal and uniform.

Model simulation and presentation of results

The base-case analyses were conducted for women aged 70, 75, and 80 years either with a BMD T-score≤−2.5 SD or with prevalent vertebral fractures using Monte-Carlo simulations using a decision analysis software (TreeAgePro 2006 Suite, release 0.4, TreeAge Software). Two hundred thousand first-order trials were performed for each analysis and guarantee a high stability of the results. The incremental cost-effectiveness ratio (ICER) was then computed as the difference between strontium ranelate and no treatment in terms of total costs divided by the difference between them in terms of effectiveness, expressed in accumulated QALYs. It represents the cost of strontium ranelate per one QALY gained.

Univariate sensitivity analyses were also run with 200,000 trials. Due to computation burden when the first-order and second-order Monte-Carlo simulations are combined, the number of trials was reduced to 25,000 for probabilistic sensitivity analyses. This number was however sufficient for a reasonable stability of the results. The model was run 150 times and parameter values were randomly selected from their respective distributions for each simulation. Cost-effectiveness acceptability curves were then constructed from the incremental cost and QALYs between alternatives for the 150 simulations. They show the probability that strontium ranelate is cost-effective compared to no treatment for a range of decision makers' willingness to pay per QALY.

Results

Base-case analyses

The lifetime costs, QALYs, and ICERs for strontium ranelate compared to no treatment are presented in Table 2 according to age and population. The cost per QALY gained of strontium ranelate decreased progressively with increasing age and did not markedly differ between the two populations. At the age of 80 years, strontium ranelate was found to be cost-saving, meaning that treatment cost was less than averted costs of treating osteoporotic fractures. At 70 years of age, the results were highly sensitive to the relative risk of hip fracture during therapy. When assuming a lower hip fracture efficacy (additional scenario), the costs per QALY gained were greatly increased in both populations.

Univariate sensitivity analyses

The results of this study were sensitive to adherence to therapy (Fig. 1). When assuming adherence similar to bisphosphonate's adherence for women with a BMD T-score≤−2.5 SD, the costs per QALY gained of strontium ranelate versus no treatment were respectively €20,622, €13,577, and €7,443 at the ages of 70, 75, and 80 years. These values were €30,338, €20,220, and €4,670 for women with prevalent vertebral fractures.

Other univariate sensitivity analyses showed the estimated ICURs to be modestly sensitive to changes in fracture cost and fracture disutility (Table 3) and quite sensitive to discount rates and changes in fracture risk. For women with a BMD T-score of –2.5 and without a prior fracture, the cost per QALY gained of strontium ranelate was estimated at €39,217 and €44,211 at the ages of 70 and 80 years, respectively. Small changes in therapy cost, fracture efficacy, and offset time had a modest effect on the cost-effectiveness of strontium ranelate. When assuming a QALY increase during therapy or no differences in monitoring costs between alternatives, the costs per QALY gained of strontium ranelate were reduced.

Probabilistic sensitivity analyses

The probability that strontium ranelate is cost-effective compared to no treatment increased with decision makers' willingness of pay per QALY and with increasing starting age of treatment (Fig. 2). At a willingness to pay of €40,000 per QALY, strontium ranelate was cost-effective in more than 83.3% of the cases, irrespective of age and population. In the additional scenario, these probabilities were 24.7% and 25.3% respectively for women with a BMD T-score≤ −2.5 SD and with prevalent vertebral fractures. The

Table 2 Lifetime costs, QALYs, and incremental cost-effectiveness ratio (cost in € per QALY gained) of strontium ranelate versus no treatment according to age and population

	BMD T-score≤−2.5 SD			Prevalent vertebral fractures		
	No treatment	Strontium	Incremental values	No treatment	Strontium	Incremental values
Age 70 years						
Costs, €	11,443	12,267	824	10,201	11,473	1,272
QALYs	10.3261	10.3807	0.0546	10.2525	10.3068	0.0543
ICER, €		15,096			23,426	
Age 70 years—additional scenario						
Costs, €	11,443	13,060	1,617	10,201	12,161	1,959
QALYs	10.3261	10.3568	0.0307	10.2525	10.2881	0.0356
ICER, €		52,669			55,041	
Age 75 years						
Costs, €	11,354	11,037	317	10,353	10,841	488
QALYs	8.0105	8.0563	0.0458	7.9635	8.0138	0.0503
ICER, €		6,913			9,698	
Age 80 years						
Costs, €	9,837	9,912	−75	10,116	10,062	−54
QALYs	5.8893	5.9120	0.0227	5.8498	5.8839	0.0341
ICER, €		Cost-saving			Cost-saving	

ICER is defined as the difference between strontium ranelate and no treatment in terms of costs divided by the difference between them in terms of QALYs

BMD bone mineral density, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

probabilities that strontium ranelate are cost-saving increased with age and were approximately 57% and 25% at the ages of 80 and 75 years, respectively.

Discussion

Strontium ranelate is the first agent of a new therapeutic class in osteoporosis, which both decreases bone resorption and stimulates bone formation [37]. In clinical trials, strontium ranelate was shown to be safe and to significantly reduce the risk of vertebral and non-vertebral fractures in a wide scatter of patients and over a long-period of time [4–

7]. Strontium ranelate has therefore the potential to be a first line treatment for osteoporosis. For health care decision makers, it is also important to know whether it represents a good value for money compared to other relevant alternatives. Cost-effectiveness analysis is one important input into the decision-making process.

There are actually no threshold values in Belgium below which an intervention can be considered cost-effective [38]. In the UK, the NICE suggest a value of £30,000 (approximately €39,000) per QALY gained [39], near to the ceiling ratio of €40,000 per QALY suggested in Sweden for cost-effectiveness analyses in osteoporosis [40]. In our base-case analysis, the cost per QALY gained of strontium

Fig. 1 Cost (in €) per QALY gained of strontium ranelate versus no treatment according to age and adherence to therapy. *AS* additional scenario, *BMD* bone mineral density, *QALY* quality adjusted life-year
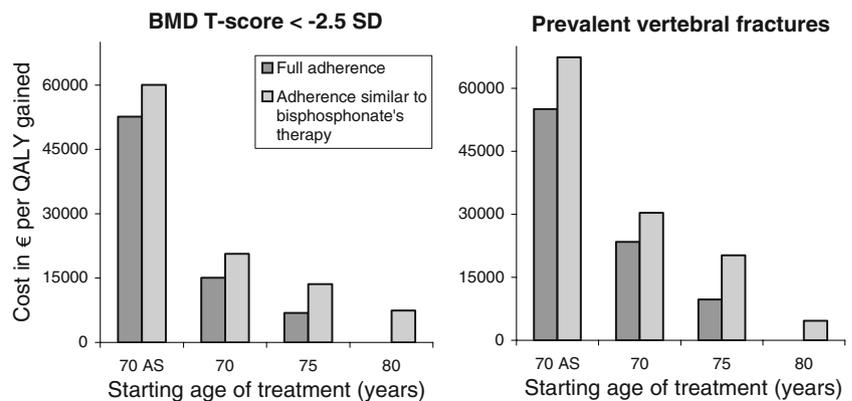
Table 3 Cost in € per QALY gained of strontium ranelate versus no treatment: univariate sensitivity analyses for women aged 70 and 80 years

	BMD T-score≤−2.5 SD		Prevalent vertebral fractures	
	70 years	80 years	70 years	80 years
Base case	15,096	CS	23,426	CS
Model parameters and assumptions				
Discount rates 3% (costs and effects)	18,017	CS	25,560	CS
Discount rates 5% (costs and effects)	26,732	4,347	34,123	5,989
0.7 time base-case fracture disutility	19,520	CS	29,863	CS
0.7 time base-case fracture costs	22,335	23,722	28,046	16,065
0.7 time base-case fracture risk	35,809	39,902	36,054	23,598
BMD T-score of –2.5 SD	39,217	44,211	–	–
Intervention				
No monitoring cost	11,216	CS	19,524	CS
Therapy cost 10% higher	19,219	5,591	27,569	4,337
Treatment efficacy 10% lower	20,550	4,968	29,155	7,518
Offset time 3 years	23,779	7,575	29,194	6,489
Offset time 7 years	10,125	CS	16,548	CS
QALY increase by 1% during therapy	9,433	CS	11,324	CS

BMD bone mineral density, *CS* cost-saving, *QALY* quality-adjusted life-year

ranelate compared to no treatment was below these ceiling ratios for all ages and for both populations. Moreover, sensitivity analyses showed that strontium ranelate was cost-effective even under assumptions of reduced adherence to therapy and over a wide range of assumptions related to model parameters and intervention. Probabilistic sensitivity analyses also showed that, at a willingness to pay of €40,000 per QALY, strontium ranelate was cost-effective in more than 83.3% of the cases irrespective of age and population. However, the cost-effectiveness of strontium ranelate was very sensitive to relative risk of hip fracture during therapy. When assuming a lower hip fracture reduction efficacy (alternative scenario), strontium ranelate was not cost-effective at 70 years of age.

Our results are consistent with those from the cost-effectiveness study of Borgström et al. [30] which suggested that a 3-year strontium ranelate was cost-effective, compared to no treatment, in the treatment of

Swedish postmenopausal women with low BMD and who are similar to patients included in the TROPOS and Spinal Osteoporosis Therapeutic Intervention trials. In our study, we specifically assessed the cost-effectiveness in the target populations for routine use of the product (i.e. in case of BMD T-score below –2.5 SD or in case of prevalent vertebral fractures).

Ideally, the cost-effectiveness of a drug therapy should be compared to the most relevant alternative treatment. Other osteoporotic treatments are available and have been shown to be cost-effective compared to no treatment in other setting, such as bisphosphonates therapies (i.e. alendronate, risedronate, and etidronate) and raloxifene [40–43]. It would have been useful to compare strontium ranelate with these drugs in the same analysis. However, the value of an incremental analysis between osteoporosis medications could be questionable because no head to head comparisons of interventions are available [42]. Clinical

Fig. 2 Cost-effectiveness acceptability curves for strontium ranelate. *BMD* bone mineral density, *AS* additional scenario, *QALY* quality adjusted life-year
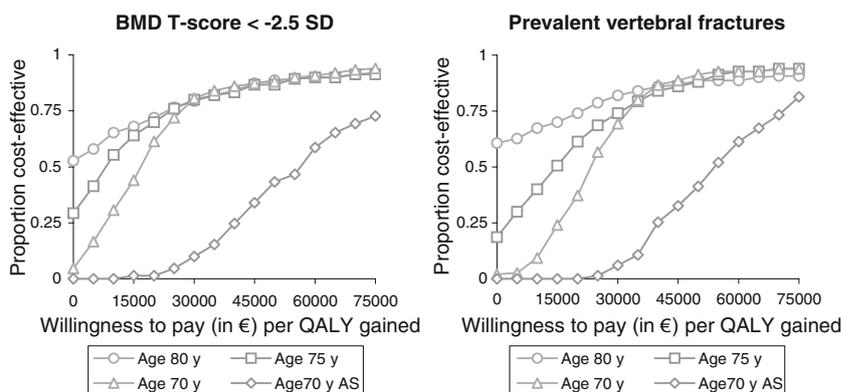
trials compared treatment with placebo and may substantially differ in terms of populations and design, making it difficult to assess the relative efficacy between treatments. No treatment has therefore been the most widely used comparator and has been considered as the most relevant comparator for cost-effectiveness analyses [44]. We therefore estimated in this study the cost-effectiveness of strontium ranelate compared to no treatment, on a basis of calcium/vit D supplementation if needed. Moreover, there have been no published reports of data obtained over 5 years in studies designed with fracture assessment as the primary end point [5]. To inform decision makers about the relative efficiency of strontium ranelate compared to other treatments, further researches are needed by making indirect comparisons.

Cost-effectiveness analysis is a useful tool to inform policy makers about the economic value of medical interventions but decision makers have to combine this information with their preferences and with possible budgets constraints [45]. The ultimate decision to reimburse or not reimburse a drug is multifactorial and depends on many aspects that may be important from a health policy perspective. As such, budget impact analysis also represents an essential part of decision making and should also be performed [46].

There are other potential limitations to our study. First, the target populations in our model was not identical to the population included in the clinical trial but were consistent with the target population for routine use of the product [11]. Therefore, the applicability of fracture reduction efficacy may be uncertain, in particular for hip fracture because this fracture risk reduction was assessed in a subgroup of patients aged 74 years and older. An additional scenario has therefore been performed for women aged 70 years including a lower hip fracture risk reduction. However, our potentially non-conservative assumption could be compensated by other advantages of strontium ranelate not included in the model. So strontium ranelate was shown to reduce the progression of radiographical spinal osteoarthritis and back pain in women with osteoporosis and spinal back pain [47] and to have beneficial effects on quality of life in women with postmenopausal osteoporosis compared with placebo [48]. The effects on quality of life were assessed using the QUALIOST questionnaire which cannot be translated into utility values and could therefore not be directly used in cost-utility analyses. Second, analyses were assessed for all women below the threshold of osteoporosis in order to estimate the cost-effectiveness in the entire population of patients. We have not identified a BMD *T*-score under which strontium ranelate would be cost-effective. However, we have shown in a sensitivity analysis that the cost-effectiveness of strontium ranelate was near to €40,000 per QALY gained at 70 and 80 years of age for women with a BMD *T*-score

of –2.5 and without a prior fracture. Third, our analysis was restricted to women with osteoporosis aged 70 years and older. Strontium ranelate was also shown to reduce the risk of vertebral fractures in women with osteopenia [7] and in young postmenopausal women with severe osteoporosis [49]. The cost-effectiveness of strontium ranelate in such populations requires further investigations. Fourthly, adherence to strontium ranelate in general clinical practice has not yet been documented. Further researches are therefore needed to assess adherence to strontium ranelate and the relationship between adherence to strontium ranelate and fracture risk.

The transferability of our results across jurisdictions could also be problematic. There are many reasons why the cost-effectiveness of health technologies might vary from place to place including the incidence of the disease, the availability of health resources, clinical practice patterns, and relative prices [50]. Analyses need to be performed for each setting and should use local data (e.g. fracture costs, fracture incidence). However, it is likely that strontium ranelate will be cost-effective in jurisdictions with similar characteristics than those retained in our analysis.

In conclusion, the results of this study suggested that long-term treatment with strontium ranelate over 5 years is cost-effective compared to no treatment for postmenopausal osteoporotic women over 70 years of age. Strontium ranelate represents a safe, effective, and cost-effective first line treatment for postmenopausal women with osteoporosis over the long term.

References

1. Boonen S, Body JJ, Boutsen Y et al (2005) Evidence-based guidelines for the treatment of postmenopausal osteoporosis: a consensus document of the Belgian Bone Club. Osteoporos Int 16:239–254

2. Lyles KW, Colon-Emeric CS, Magaziner JS et al (2007) Zoledronic Acid in Reducing Clinical Fracture and Mortality after Hip Fracture. N Engl J Med 357:1799–1809, nihpa40967

3. Harris ST, Reginster JY, Harley C et al (2009) Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: The eValuation of IBandronate Efficacy (VIBE) database fracture study. Bone. doi:10.1016/j.bone.2009.01.002

4. Meunier PJ, Roux C, Seeman E et al (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 350:459–468

5. Reginster JY, Felsenberg D, Boonen S et al (2008) Effects of long-term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum 58:1687–1695

6. Reginster JY, Seeman E, De Vernejoul MC et al (2005) Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 90:2816–2822

7. Seeman E, Devogelaer JP, Lorenc R et al (2008) Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. J Bone Miner Res 23:433–438

8. Hoffmann C, Graf von der Schulenburg JM (2000) The influence of economic evaluation studies on decision making. A European survey. The EUROMET group. Health Policy 52:179–192

9. Drummond M, Dubois D, Garattini L et al (1999) Current trends in the use of pharmacoeconomics and outcomes research in europe. Value Health 2:323–332

10. Hiligsmann M, Ethgen O, Bruyère O, et al (2009) Development and validation of a Markov microsimulation model for the economic evaluation of treatments in osteoporosis. Value Health. doi:10.1111/j.1524-4733.2008.00497

11. Cleemput I, Crott R, Vrijens F et al (2008) Recommandations provisoires pour les évaluations pharmacoéconomiques en Belgique. Health Technology Assessment (HTA). Bruxelles: Centre Fédéral d'Expertise des Soins de Santé (KCE). KCE reports vol. 78B (D/2008/10.273/24)

12. Dere W, Avouac B, Boers M et al (1998) Recommendations for the health economics analysis to be performed with a drug to be registered in prevention or treatment of osteoporosis. Calcif Tissue Int 63:93–97

13. Reginster JY, Gillet P, Ben Sedrine W et al (1999) Direct costs of hip fractures in patients over 60 years of age in Belgium. Pharmacoeconomics 15:507–514

14. Autier P, Haentjens P, Bentin J et al (2000) Costs induced by hip fractures: a prospective controlled study in Belgium. Belgian Hip Fracture Study Group. Osteoporos Int 11:373–380

15. Reginster JY, Gillet P, Gosset C (2001) Secular increase in the incidence of hip fractures in Belgium between 1984 and 1996: need for a concerted public health strategy. Bull World Health Organ 79:942–946

16. Gabriel SE, Tosteson AN, Leibson CL et al (2002) Direct medical costs attributable to osteoporotic fractures. Osteoporos Int 13:323–330

17. Melton LJ 3rd, Gabriel SE, Crowson CS et al (2003) Cost-equivalence of different osteoporotic fractures. Osteoporos Int 14:383–388

18. Hiligsmann M, Ethgen O, Richy F et al (2008) Utility values associated with osteoporotic fracture: a systematic review of the literature. Calcif Tissue Int 82:288–292

19. Hiligsmann M, Bruyère O, Ethgen O et al (2008) Lifetime absolute risk of hip and other osteoporotic fracture in Belgian women. Bone 43:991–994

20. Kanis JA, Johnell O, Oden A et al (2000) Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. Bone 27:585–590

21. Looker AC, Wahner HW, Dunn WL et al (1998) Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 8:468–489

22. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312:1254–1259

23. Johnell O, Kanis JA, Oden A et al (2005) Predictive value of BMD for hip and other fractures. J Bone Miner Res 20:1185–1194

24. Klotzbuecher CM, Ross PD, Landsman PB et al (2000) Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 15:721–739

25. Kanis JA, Johnell O, De Laet C et al (2004) A meta-analysis of previous fracture and subsequent fracture risk. Bone 35:375–382

26. Caulin F, Kanis JA, Johnell O et al (2002) Optimal age for preventing osteoporosis after menopause depends on effects of stopping treatment. Bone 30:754–758

27. Jonsson B, Kanis J, Dawson A et al (1999) Effect and offset of effect of treatments for hip fracture on health outcomes. Osteoporos Int 10:193–199

28. Meunier PJ, Roux C, Ortolani S et al (2008) Effects of long-term strontium ranelate treatment on vertebral fracture risk in postmenopausal women with osteoporosis. doi:10.1007/s00198-008-0825-6

29. Zethraeus N, Borgstrom F, Strom O et al (2007) Cost-effectiveness of the treatment and prevention of osteoporosis—a review of the literature and a reference model. Osteoporos Int 18:9–23

30. Borgstrom F, Jonsson B, Strom O et al (2006) An economic evaluation of strontium ranelate in the treatment of osteoporosis in a Swedish setting: based on the results of the SOTI and TROPOS trials. Osteoporos Int 17:1781–1793

31. Lekkerkerker F, Kanis JA, Alsayed N et al (2007) Adherence to treatment of osteoporosis: a need for study. Osteoporos Int 18:1311–1317

32. Rabenda V, Mertens R, Fabri V et al (2008) Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. Osteoporos Int 19:811–818

33. Cramer JA, Roy A, Burrell A et al (2008) Medication compliance and persistence: terminology and definitions. Value Health 11:44–47

34. Belgian Center for Pharmacotherapeutic Information, 2008, Available from: http://www.cbip.be/GGR/MPG/MPG_NJ.cfm#MP_2583

35. Kanis J, Burlet N, Cooper C et al (2008) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 19:399–428

36. Briggs A, Sculpher M, Claxton K (2006) Modelling methods for health economic evaluation. Oxford University Press, New York

37. Neuprez A, Hiligsmann M, Scholtissen S et al (2008) Strontium ranelate: the first agent of a new therapeutic class in osteoporosis. Adv Ther 25:1235–1256

38. Cleemput I, Neyt M, Thiry N et al (2008) Valeurs seuils pour le rapport coût-efficacité en soins de santé. Health Technology Assessment (HTA). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE);2008. KCE Reports 100B (D/2008/10.273/95)

39. Raftery J (2001) NICE: faster access to moder treatments? Analysis of guidance on health technologies. Br Med J 323:1300–1303

40. Strom O, Borgstrom F, Sen SS et al (2007) 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 18:1047–1061

41. Borgstrom F, Johnell O, Kanis JA et al (2004) Cost effectiveness of raloxifene in the treatment of osteoporosis in Sweden: an economic evaluation based on the MORE study. Pharmacoeconomics 22:1153–1165

42. Kanis JA, Adams J, Borgstrom F et al (2008) The cost-effectiveness of alendronate in the management of osteoporosis. Bone 42:4–15
43. Stevenson M, Lloyd Jones M, De Nigris E et al (2005) A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess 9:1–160
44. Borgstrom F, Kanis JA (2008) Health economics of osteoporosis. Best Pract Res Clin Endocrinol Metab 22:885–900
45. Al MJ, Feenstra T, Brouwer WB (2004) Decision makers' views on health care objectives and budget constraints: results from a pilot study. Health Policy 70:33–48
46. Mauskopf JA, Sullivan SD, Annemans L et al (2007) Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices—budget impact analysis. Value Health 10:336–347
47. Bruyere O, Delferriere D, Roux C et al (2008) Effects of strontium ranelate on spinal osteoarthritis progression. Ann Rheum Dis 67:335–339
48. Marquis P, Roux C, de la Loge C et al (2008) Strontium ranelate prevents quality of life impairment in post-menopausal women with established vertebral osteoporosis. Osteoporos Int 19:503–510
49. Roux C, Fechtenbaum J, Kolta S et al (2008) Strontium ranelate reduces the risk of vertebral fracture in young postmenopausal women with severe osteoporosis. Ann Rheum Dis 67:335–339
50. Drummond M, Barbieri M, Cook J et al (2009) Transferability of economic evaluations across juridictions: ISPOR good research practices task force report. Value Health [Epub Ahead of Print]