ABSTRACT Managed care organizations (MCOs) are responding to rising pharmaceutical expenditures by imposing cost-containment measures, including the adoption of cost-effectiveness guidelines to assess the economic and clinical value of new therapies. Osteoporosis is a large and growing disease category for which cost-effectiveness analyses might help minimize total system costs. Our economic evaluation of bisphosphonate therapy found that the adoption of risedronate (Actonel®), compared with alendronate (Fosamax®) for the treatment of postmenopausal osteoporosis patients at high risk of fracture, may produce lower costs and better outcomes over a three-year period. When patients are treated for three years with risedronate and the reduction in lifetime osteoporosis costs related to chronic disability is considered, the acquisition cost of risedronate to a MCO is fully offset.

KEY WORDS: osteoporosis, postmenopausal women, cost-effectiveness, cost, quality-adjusted life years

INTRODUCTION

Postmenopausal osteoporosis (PMO) is characterized by reduced bone mass leading to an increased risk of fracture. The prevalence of PMO increases with age from approximately 6% at age 50 to over 50% above age 80. The incidence of osteoporotic fractures follows a similar pattern, with wrist fractures peaking at approximately age 70, and vertebral and hip fractures at age 85. Fractures are associated with significant reductions in quality of life caused by disability, pain, and deformity, and they constitute an important cause of death among the elderly.

The high prevalence of osteoporosis, coupled with its significant health consequences, makes effective prevention and treatment a leading concern for managed care organizations (MCOs). Current treatment options include bisphosphonates, calcitonins, and selective estrogen receptor modulators (SERMs). In the U.S., bisphosphonates are the most widely prescribed, with alendronate having the largest market share. Risedronate is a more recently introduced bisphosphonate, which has been shown to significantly reduce the incidence of vertebral and nonvertebral fractures.

As intervention options grow in all therapeutic areas, MCOs are increasingly seeking ways to equitably allocate resources to achieve maximum health care benefits for their subscribers. One approach is to examine the cost-effectiveness of available therapies to prioritize spending. In this study, efficacy data drawn from clinical trials were combined with epidemiological, resource use, and quality-of-life data to assess the cost-effectiveness of competing bisphosphonate therapies within a Markov state-transition model of PMO.

Such economic models are widely used for evaluating pharmaceutial interventions when comparative trials are unavailable and their conduct is prohibitively expensive or would result in unacceptable treatment delays. Models integrate the best available data into an analytic framework that allows head-to-head comparisons of alternative therapies in relevant population subgroups. Furthermore, they are particularly useful in assessing the full impact of therapy in chronic diseases for which treatment might have clinical, quality-of-life, or economic impacts that extend beyond the time horizon of the clinical trials.

OBJECTIVE

The purpose of this study was to evaluate the short-term cost-effectiveness and budget impact of risedronate therapy compared with alendronate therapy in the treatment of patients with PMO at high risk of fracture based on T-score at or below –2.5 and a prevalent vertebral fracture.

METHODS

Patient Population

Our base case analysis consisted of a hypothetical cohort of 65-year-old-women with low bone mineral density (BMD) (i.e., BMD of 2.5 or more standard deviations [SD] below the young adult mean) and a prevalent vertebral fracture. We assume that 21% of 65- to 69-year-olds fall into this study population.

Model Overview

A fracture incidence-based model of the natural history of osteoporosis was developed to estimate the cost-effectiveness and budget impact outcomes for patients at high risk of fracture treated with risedronate and alendronate therapies. A fracture incidence-based model was selected over a BMD-based model because this type of model uses fracture incidence rates to model fracture occurrence, as opposed to an intermediate clinical endpoint such as changes in BMD over time. The model was developed under the guidance of a committee of academic advisors who had independent control over all design and methodological decisions. In accordance with health economic guidelines, the model was transparent and underwent extensive validation. A modeling approach was chosen...
for this analysis because of the lack of head-to-head trials comparing the therapies under evaluation in this patient subgroup.

Details of the model design, structure, and assumptions have been described previously.16 In summary, it is a Markov state-transition model14 in which patients can move between several short- and long-term health outcome states over time (Figure 1). Long-term health states include Healthy, Healthy Post-Vertebral Fracture, Healthy Post-Hip Fracture, Healthy Post-2nd Hip Fracture, and Death. Short-term health states, which patients enter and leave within any given year, are Vertebral Fracture, Hip Fracture, and 2nd Hip Fracture. These short-term states are used to capture the acute-care costs and decrements in quality of life that are associated with fracture.

The model permits movement between health states annually according to state-dependent transition probabilities (i.e., age-specific fracture incidence and mortality rates) that were derived from best available observational data. Treatment effects are modeled as a relative risk (RR) reduction in fracture rates, whereas a patient population at increased risk of fracture caused by the presence of a variety of risk factors can be modeled by direct modification of fracture rates via RRs. Outputs include frequency of fractures, health care costs, and decrements in quality of life that are associated with fracture.

The following sections describe the input data used in the model. For all model inputs, the best available data sources were consulted and consisted primarily of published values from clinical trials, economic studies, observational studies, and epidemiological databases. Where uncertainty existed or assumptions were required for specific data inputs, sensitivity analyses were conducted on those input values. The base case values and data sources are provided in Table 1.

### Hip Fracture

Age-specific incidence rates for hip fracture were obtained from a study of the general female population in Rochester, Minnesota, which includes both patients with and without POM.18 Our study focused on treatment of POM patients at high risk of fracture; therefore, fracture rates were adjusted to reflect the increased risk of new fractures in patients with low BMD and a prevalent vertebral fracture.

The RR associated with a prevalent vertebral fracture was adjusted based on the prevalence of the risk factor in the general female population to estimate the RR in our target population compared to the general female population.16 For example, if the RR of hip fracture in a 65-year-old population with a previous vertebral fracture, compared to a population without a previous vertebral fracture, is 1.917 and the prevalence of vertebral fracture in 65-year-olds is 14.3%, then the RR of hip fracture in patients with a previous vertebral fracture, compared to the general population, is 1.7 (1.9/14.3).

The RR reported per SD decrease in BMD was also adjusted to account for the proportion of women in the age-specific general population with BMD at or below that of the target population. For example, with increasing age, the average BMD of the general population decreases, resulting in a greater proportion of the population with a T-score less than or equal to −2.5. As this occurs, the fracture rate increases, resulting in a smaller RR of fracture between the target population and the general population.

Following these adjustments, the RRs were combined multiplicatively with the population fracture rates to approximate rates of hip and vertebral fracture in a population with these risk factors.16 The ten-year and lifetime risks of hip fracture in the target population were estimated to be 21.2% and 62.5% compared with 3.6% and 18.3% for a 65-year-old in the general population. Ideally, the predicted lifetime risk for the target population would be compared to published risks for the same populations. However, there are limited data on lifetime risk in women at high risk of fracture. A report by the World Health Organization provided lifetime risks for a 50-year-old woman with various levels of BMD measured at the hip.18 In the portion of the population with the lowest BMD (i.e., 0.80 to 0.89, 0.70 to 0.79, 0.60 to 0.69 and <0.60 g/cm²) the lifetime risk of fracture was estimated to be between 40% and 51% (40%, 47%, 50%, and 51%, respectively). Calculation of T-scores from this source is not possible because the mean and SD for the BMD of young adults is not reported for the measurement instrument used and can vary substantially between machines.

Lifetime risks for 50-year-old populations with low BMD could not be predicted by the model because of a lack of data required to calculate the RR of hip fracture of 50-year-olds with low BMD. For these calculations, RR values and risk factor prevalence data were obtained from the Study of Osteoporotic Fracture database (Dennis Black, personal communication). Age-specific BMD data were taken from the National Health and Nutrition Examination Survey (NHANES III) study.19 Fracture rates were adjusted to account only for risk factors in the starting cohort; no further adjustments were made for fractures occurring during the model.

Figure 1. Allowable state transitions caused by fractures (Fx) based on starting state.
Efficacy values (RR of hip fracture) of 0.40 and 0.49 were used for patients treated with risedronate and alendronate, respectively, and were obtained from randomized clinical trials with patient populations similar to the base case cohort.6,20 The adjusted age-specific fracture rates were multiplied by these values to estimate fracture rates in the treated cohorts. Excess mortality in the year of hip fracture was considered in the model.21

The first-year costs following a hip fracture were assumed to be $36,864, and included expected costs of acute inpatient care (hospital facility, inpatient physician, emergency room, readmissions), long-term care (skilled nursing facility, disability-related care) and outpatient care (rehabilitation care, outpatient physician visits, home health care). The hip fracture cost estimates were derived from previous studies, updated to the year 2000, using the medical care component of the consumer price index.4,22,23 These included acute care hospital costs of $16,293 for women aged 65 to 74 ($18,131 updated to the year 2000).23

Expected hip fracture costs in subsequent years were assumed to be $3,832 and included disability-related costs of $1,1654 and long-term care costs in skilled nursing facilities of $2,667. The latter cost component was derived by multiplying the annual cost of nursing home care ($38,431) by the probability of a hip fracture patient requiring permanent nursing care (7%).4

Utility weights were applied to each health state to allow for the calculation of quality-adjusted life years (QALYs). Utilities reflect how quality of life in a health state is valued on a scale from 0 (death) to 1 (perfect health). The age-specific utility weight for 65- to 69-year-old women in the general population was 0.833.24 This utility value was reduced upon occurrence of a fracture by 0.18 in the year of a hip fracture25 and 0.09 in all subsequent years.26 For women with both hip fracture and vertebral fracture, the utility reduction was 0.55 in the year of the hip fracture and 0.09 in all subsequent years.25

### Vertebral Fracture
As with hip fracture, vertebral fracture rates for the general population were adjusted to reflect a PMO population.27 Efficacy values (in terms of relative risk of fracture) of 0.51 and 0.53 were used for patients treated with risedronate28 or alendronate,20 respectively. These efficacy rates were obtained from randomized clinical trials with similar patient populations as the base case cohort. Excess mortality caused by vertebral fractures was not incorporated because of the lack of comprehensive data on the degree of increased risk of death.

Therapy Data

### Therapy Data

<table>
<thead>
<tr>
<th>Efficacy of untreated fracture (RR)**</th>
<th>Hip Fracture</th>
<th>Vertebral Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risedronate (Actonel®)</td>
<td>0.40*</td>
<td>0.51**</td>
</tr>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>0.49**</td>
<td>0.53**</td>
</tr>
</tbody>
</table>

Notes:

* Unit cost was adjusted downward to reflect the proportion of patients seeking medical care and the proportion of clinical cases admitted to acute care hospitals.

** Relative risk (RR) of 0.40 indicates a reduction of 60% in fracture incidence rate.

*** Includes only acquisition costs.
Bisphosphonate Therapies

Other Fracture Types

In randomized clinical trials, risedronate significantly reduced the number of nonvertebral fractures (defined as a composite of six bone sites: leg, humerus, clavicle, pelvis, hip and wrist) between 36% and 39%, whereas alendronate produced a nonsignificant reduction in fractures of 21%.6,20 However, sufficient data were lacking on the incidence and expected costs of non-hip/non-vertebral fractures; therefore, we excluded these types of fractures from the analysis. Fractures of the wrist or forearm were also excluded from the analysis because neither risedronate nor alendronate had consistent and statistically significant efficacy values across their clinical trials.

COST-EFFECTIVENESS AND BUDGET IMPACT ANALYSIS

The cost-effectiveness of each therapy was assessed in terms of the incremental cost per hip fracture averted and per QALY gained. The cost-effectiveness ratios were calculated by dividing the difference in total discounted costs between two treatment groups (e.g., A and B) by the difference in discounted treatment effectiveness.

\[
\frac{\text{Costs}_A - \text{Costs}_B}{\text{Effects}_A - \text{Effects}_B}
\]

In the base case analysis, both costs and outcomes were discounted at a rate of 3%.13 Costs included all fracture-related costs in the year of fracture and all subsequent years as well as the cost of therapy over the entire observation period. In addition to compar-

### Table 2 Parameter Values Used in the Sensitivity Analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fracture Costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of Fracture</td>
<td>Subsequent Years</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>$27,648</td>
<td>$2,874</td>
</tr>
<tr>
<td>High</td>
<td>$46,080</td>
<td>$4,790</td>
</tr>
<tr>
<td>Vertebral Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>$1,410</td>
<td>$53</td>
</tr>
<tr>
<td>High</td>
<td>$2,350</td>
<td>$89</td>
</tr>
<tr>
<td><strong>Utility Values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of Fracture</td>
<td>Subsequent Years</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.09</td>
<td>0.045</td>
</tr>
<tr>
<td>High</td>
<td>0.27</td>
<td>0.135</td>
</tr>
<tr>
<td>Vertebral Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>High</td>
<td>0.24</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Therapy Discontinuation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 3 months</td>
<td>25%</td>
<td>Analysis of General Practice Research Database38</td>
</tr>
<tr>
<td>Rest of 1st year</td>
<td>23%</td>
<td>Data on file, Procter &amp; Gamble Pharmaceuticals</td>
</tr>
<tr>
<td>During 2nd year</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>During 3rd year</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Cumulative over 3 years</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate (Actonel®)</td>
<td>Hip Fracture</td>
<td>Vertebral Fracture</td>
</tr>
<tr>
<td>80%, 20%</td>
<td>64%, 27%</td>
<td>McClung et al., 20016/ Reginster et al., 200028</td>
</tr>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>99%, 23%</td>
<td>59%, 32%</td>
</tr>
<tr>
<td><strong>Relative Risk of Fracture</strong></td>
<td>Both hip and vertebral</td>
<td>4, 5, 6, 7</td>
</tr>
<tr>
<td><strong>Observation Period</strong></td>
<td>Lifetime (death or age 100 years)</td>
<td></td>
</tr>
<tr>
<td><strong>Starting Age of Therapy</strong></td>
<td>55, 60, 70, 75 years</td>
<td></td>
</tr>
</tbody>
</table>
ing risedronate to alendronate, both therapies were compared to an untreated cohort. Total budgetary impacts of each therapy over the three-year period were also calculated using the discounted costs.

Sensitivity Analyses
To assess the sensitivity of the results to the uncertainty in the input variables, one-way sensitivity analyses were conducted. Variables explored in these analyses included fracture costs, RR, utility values, therapy efficacy, therapy discontinuation rates, and patient age (see Table 2 for data ranges). The lifetime risks of hip fracture for a population with a RR of 4.0 and 5.0 were estimated as 49.6% and 56%, respectively. In addition to these analyses, a sensitivity analysis was conducted in which the base case three-year treatment duration was used, but the observation period for costs and consequences was extended to include the lifetime of patients in the cohort (defined as death or 100 years of age). This analysis was particularly important as it illustrates the long-term treatment benefits in terms of cost-savings and QALYs gained, and is consistent with methodologies employed previously in cost-effectiveness evaluation guidelines22,23 and with previous analyses of osteoporosis12,23,24.

RESULTS
Over the three-year period, risedronate produced greater reductions in fractures compared to alendronate. Patients treated with risedronate experienced 23 hip and 111 vertebral fractures (134 total fractures) per 1,000 patients (Table 3). In contrast, a total of 28 hip fractures and 115 vertebral fractures per 1,000 patients (for a total of 143 fractures) were experienced with alendronate. Among the 1,000 patients in the untreated cohort, there were 58 hip fractures (three-year risk of 5.8%) and 217 vertebral fractures (three-year risk of 21.7%). Treatment with risedronate also resulted in higher QALYs than alendronate (2.359 versus 2.356 per 1,000 patients, respectively) and placebo (2.321 per 1,000 patients). The total costs were lowest for the untreated cohort, followed by risedronate and alendronate.

Cost-Effectiveness Analysis
When risedronate was compared to the least expensive option (no therapy), the incremental cost per hip fracture avoided was $16,158, whereas the incremental cost per QALY gained was $17,649. Prior to the availability of risedronate, a comparison of alendronate to no therapy would have been appropriate and would have resulted in an incremental cost per hip fracture averted of nearly $36,000, whereas the incremental cost per QALY gained was over $30,000. The use of risedronate instead of alendronate was found to produce a “dominant” situation in which risedronate resulted in lower overall costs and better outcomes. In this situation, a cost-effectiveness ratio comparing to alendronate was not calculated because alendronate is considered to be dominated by risedronate (Table 3).

Budget Impact Analysis
Table 4 presents the budget impact analysis for the base case scenario over three years. In contrast to an untreated group, treating patients with either risedronate or alendronate led to lower inpatient care, long-term care, and outpatient care costs. Drug acquisition costs of approximately $2,400 for alendronate and $2,200 for risedronate led to an increase in overall budget per patient compared to no therapy, which was partially offset by cost savings related to

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost (per Patient)</th>
<th>QALYs (per Patient)</th>
<th>No. of Fractures per 1000 Patients</th>
<th>Incremental Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vertebral</td>
<td>Hip</td>
</tr>
<tr>
<td>None</td>
<td>$2,720</td>
<td>2.321</td>
<td>217</td>
<td>58</td>
</tr>
<tr>
<td>Risedronate</td>
<td>$3,331</td>
<td>2.359</td>
<td>111</td>
<td>23</td>
</tr>
<tr>
<td>Alendronate</td>
<td>$3,773</td>
<td>2.356</td>
<td>115</td>
<td>28</td>
</tr>
</tbody>
</table>

Notes:
QALY = quality-adjusted life years
Dominated = lower cost and better outcomes

<table>
<thead>
<tr>
<th>Type of Care</th>
<th>No Therapy</th>
<th>Risedronate</th>
<th>Alendronate (Fosamax®)</th>
<th>No Therapy</th>
<th>Alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient Care</td>
<td>$1,568</td>
<td>$659</td>
<td>$780</td>
<td>($909)</td>
<td>($121)</td>
</tr>
<tr>
<td>Long-Term Care</td>
<td>$841</td>
<td>$345</td>
<td>$418</td>
<td>($495)</td>
<td>($72)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>$311</td>
<td>$136</td>
<td>$158</td>
<td>($175)</td>
<td>($22)</td>
</tr>
<tr>
<td>Drug</td>
<td>—</td>
<td>$2,190</td>
<td>$2,416</td>
<td>$2,190</td>
<td>($226)</td>
</tr>
<tr>
<td>Total</td>
<td>$2,720</td>
<td>$3,331</td>
<td>$3,773</td>
<td>$611</td>
<td>($442)</td>
</tr>
</tbody>
</table>

Notes:
Inpatient care includes inpatient hospital, inpatient physician, and readmission costs.
Long-term care includes costs to rehabilitation and skilled nursing facilities.
sensitivity analysis ($121 per patient) related to fracture care. Of lower acquisition costs ($226 per patient) and lower inpatient costs resulted in total cost savings of $442 per patient, primarily as a result of averted fractures. The use of risedronate instead of alendronate resulted in cost per QALY gained and cost per hip fracture averted, in contrast to no therapy, increased dramatically to approximately $90,000 and $140,000 (data not shown), respectively. Starting ages below 65 years resulted in higher ratios because of lower fracture rates at those ages, whereas the treatment of older cohorts resulted in lower ratios (Table 6).

A budget impact sensitivity analysis was conducted using the same scenarios from the cost-effectiveness analysis (Table 7). The budget impact results were consistent with the cost-effectiveness results, such that scenarios in which risedronate had the best cost-effectiveness results also had the most favorable budget impact. In most scenarios, risedronate resulted in an additional cost compared to no treatment and cost savings when compared to alendronate. Compared to not treating patients, cost savings were observed when patients aged 75 were treated with risedronate and observed for three years. Risedronate use was virtually cost-neutral compared to no therapy under two scenarios: (1) when the base case cohort of patients was given risedronate therapy for three years and followed until death or age 100 and (2) when the upper confidence limit for risedronate hip fracture efficacy (80% reduction in RR of fracture) was used (Table 7).

### DISCUSSION
Health care budgets are limited and, therefore, new therapies are increasingly required to demonstrate both clinical and economic benefits. In the case of PMO, demographic trends indicate that in the coming years a larger proportion of the population will be at risk of PMO because of advancing age, thereby placing an increased burden on MCOs to provide PMO care.

To assess the cost-effectiveness of PMO therapy, we conducted an economic analysis of two leading bisphosphonates from a MCO perspective over a three-year period. A comprehensive model of PMO was used to estimate the cost-effectiveness of these therapies in terms of cost per QALY gained, cost per hip fracture averted, and the total budget impact over a three-year period.

The results obtained indicate that risedronate is more effective at fracture prevention, and less costly, than alendronate. As a consequence, budget savings are possible for MCO plans when risedronate is prescribed instead of alendronate. Compared to no treatment, risedronate therapy provides an attractive incremental cost per gain in health. The latter comparison is provided primarily for illustrative purposes, because not treating patients is not an acceptable clinical option.

### Table 5 Cost-Effectiveness of Risedronate Compared to No Therapy from Sensitivity Analyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Incremental Cost per QALY Gained</th>
<th>Hip Fracture Averted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base Case</strong></td>
<td>$16,158</td>
<td>$17,649</td>
</tr>
<tr>
<td><strong>Fracture Costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>$26,608</td>
<td>$29,063</td>
</tr>
<tr>
<td>High</td>
<td>$5,708</td>
<td>$6,234</td>
</tr>
<tr>
<td><strong>Utility Values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>$29,763</td>
<td>$17,649***</td>
</tr>
<tr>
<td>High</td>
<td>$11,089</td>
<td>$17,649***</td>
</tr>
<tr>
<td><strong>Therapy Discontinuation</strong></td>
<td>$29,458</td>
<td>$35,044</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate (Actonel®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>$1,748</td>
<td>$1,881</td>
</tr>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>Low</td>
<td>$136,772*</td>
</tr>
<tr>
<td></td>
<td>$3,926,926*</td>
<td>High</td>
</tr>
<tr>
<td>Risedronate dominated by alendronate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relative Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>$46,250</td>
<td>$54,711</td>
</tr>
<tr>
<td>5</td>
<td>$29,190</td>
<td>$34,564</td>
</tr>
<tr>
<td>6</td>
<td>$17,854</td>
<td>$21,161</td>
</tr>
<tr>
<td>7</td>
<td>$9,788</td>
<td>$11,612</td>
</tr>
<tr>
<td><strong>Lifetime Observation Period</strong></td>
<td>$980</td>
<td>$4,578</td>
</tr>
</tbody>
</table>

Notes:
- * At 75 years, risedronate (Actonel®) is less costly and more effective than no therapy (i.e., no therapy is dominated).
The model is subject to limitations common to all decision-analytic models, in that it combines data from numerous sources, and it requires structural and data assumptions and can be subject to certain biases. The first two limitations cannot be avoided because the primary motivation for creating any decision-analytic model is to assess comparative strategies in the absence of complete data. Whenever possible, assumptions were made that reduced any potential bias toward either intervention.

The efficacy data were obtained from separate clinical trials, which included some differences in study design and patient populations. The most important differences included a lower femoral neck T-score in the risedronate group (–3.7 [or –2.8 when NHANES correction was applied] versus –2.5 in the alendronate study) and a greater number of prevalent vertebral fractures at baseline in the risedronate study.6,20,28 On the basis of these differences, it appears that the risedronate populations might have been at greater risk of fracture than the alendronate population, but it is unclear whether this would increase or decrease the potential impact of therapy. Adjustments to the reported efficacy data to correct for differences in the trial populations were not conducted because of the uncertainty regarding the impact of such differences on efficacy.

The estimates of RR of fracture in patients of various ages and T-scores are based on the best available data and produce lifetime risks of hip fracture within a reasonable range. However, the epidemiological data regarding fracture risk is still developing and some uncertainty thus exists in these parameters. The cost-effectiveness results were sensitive to RR when lowered below RR 5, but were relatively stable in the range of 5 to 7. Given the requirement for both low BMD and previous vertebral fracture in the target population, it is likely that the risk of fracture would be considerably higher than the risk in the general population, which includes patients without osteoporosis.

Because of a lack of comprehensive data on efficacy, cost, and fracture incidence data, the analysis did not include other fracture sites in the skeleton. Their exclusion results in a bias against both interventions compared to no therapy, as averting these fractures would provide additional cost and quality-of-life benefits.

The impact of therapy side effects on cost and quality of life were not included in the analysis. Neither the risedronate nor the alendronate trials reported a significant difference in adverse events compared to placebo, but the alendronate trial excluded patients with peptic-ulcer disease or dyspepsia who required daily treatment. Some observational data indicate that alendronate might cause a greater incidence of gastrointestinal side effects, compared to osteopenic and osteoporotic controls,35,36 but the majority of these events are assumed to be minor with little cost or quality-of-life implication. It is therefore assumed that the inclusion of side effects would not alter the study conclusions. Similarly, the disutility associated with taking the medications was not included but would probably have little impact on the results.

The model is subject to limitations common to all decision-analytic models, in that it combines data from numerous sources, and it requires structural and data assumptions and can be subject to certain biases. The first two limitations cannot be avoided because the primary motivation for creating any decision-analytic model is to assess comparative strategies in the absence of complete data. Whenever possible, assumptions were made that reduced any potential bias toward either intervention.

The efficacy data were obtained from separate clinical trials, which included some differences in study design and patient populations. The most important differences included a lower femoral neck T-score in the risedronate group (–3.7 [or –2.8 when NHANES correction was applied] versus –2.5 in the alendronate study) and a greater number of prevalent vertebral fractures at baseline in the risedronate study.6,20,28 On the basis of these differences, it appears that the risedronate populations might have been at greater risk of fracture than the alendronate population, but it is unclear whether this would increase or decrease the potential impact of therapy. Adjustments to the reported efficacy data to correct for differences in the trial populations were not conducted because of the uncertainty regarding the impact of such differences on efficacy.

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The base case analysis assumed no discontinuation of therapy because data are insufficient regarding continuation of osteoporosis therapies to inform the model. However, sensitivity analyses were conducted to simulate the potential impact of therapy discontinuation and revealed higher cost-effectiveness ratios owing to a decrease in clinical benefits observed over the three-year period. Al-

### Table 7 Budget Impact by Type of Care from Sensitivity Analyses

<table>
<thead>
<tr>
<th>Analysis Scenarios</th>
<th>Cost (in Thousands) (per 1,000 Patients)</th>
<th>Cost of Risedronate (in Thousands) vs.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base Case Scenario</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Therapy</td>
<td>$2,720</td>
<td>$3,331</td>
</tr>
<tr>
<td>Risedronate</td>
<td>$3,331</td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>$3,773</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative Scenarios</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 65: Lifetime Follow-up</td>
<td>$36,520</td>
<td>$36,641</td>
</tr>
<tr>
<td>Low Efficacy (A,F)</td>
<td>$2,720</td>
<td>$4,340</td>
</tr>
<tr>
<td>Low Efficacy (A)</td>
<td>$2,720</td>
<td>$4,340</td>
</tr>
<tr>
<td>Low Efficacy (F)</td>
<td>$2,720</td>
<td>$3,331</td>
</tr>
<tr>
<td>High Efficacy (A,F)</td>
<td>$2,720</td>
<td>$2,807</td>
</tr>
<tr>
<td>High Efficacy (A)</td>
<td>$2,720</td>
<td>$2,807</td>
</tr>
<tr>
<td>High Efficacy (F)</td>
<td>$2,720</td>
<td>$3,331</td>
</tr>
<tr>
<td>Therapy Discontinuation</td>
<td>$2,720</td>
<td>$3,331</td>
</tr>
<tr>
<td>Low Fracture Costs</td>
<td>$2,720</td>
<td>$3,331</td>
</tr>
<tr>
<td>High Fracture Costs</td>
<td>$2,720</td>
<td>$3,331</td>
</tr>
<tr>
<td>Low-Risk Population***</td>
<td>$872</td>
<td>$2,558</td>
</tr>
<tr>
<td>Age 55: Base Case for Age Group</td>
<td>$1,948</td>
<td>$3,028</td>
</tr>
<tr>
<td>Age 60: Base Case for Age Group</td>
<td>$1,820</td>
<td>$2,980</td>
</tr>
<tr>
<td>Age 70: Base Case for Age Group</td>
<td>$2,693</td>
<td>$3,307</td>
</tr>
<tr>
<td>Age 75: Base Case for Age Group</td>
<td>$5,083</td>
<td>$4,259</td>
</tr>
</tbody>
</table>

Notes:
A, F = efficacy scenario applied to both risedronate (Actonel® (A) and alendronate (Fosamax®) (F).
* Base case efficacy applied for alendronate.
** Base case efficacy applied for risedronate.
*** Relative risk is 2.0 for hip and 2.0 for vertebral fracture for the patient cohort.
though therapy discontinuation reduced pharmacy costs, it resulted in higher overall treatment costs because the possible foregone cost reductions from averted fractures outweighed the savings in drug acquisition costs. However, there are no data to suggest that continuation would be higher with either risedronate or alendronate.

The study utilized a three-year period to reflect interest in short-term budget implications among payers. To fully assess the impact of an intervention, however, cost-effectiveness analyses should utilize a period of time sufficient to capture all relevant subsequent effects and their associated costs. Prevention of osteoporotic fractures avoids not only the cost and quality-of-life effects of the acute event but also all subsequent effects related to permanent disability resulting from the fracture. Because the negative impact of fractures can continue for a patient’s lifetime, the disparity between treated and untreated patients increases each year after the initial event. The sensitivity analysis in which patients were treated for three years but were observed for their lifetimes indicated that inclusion of these eventual effects can almost completely offset the acquisition cost of therapy, resulting in near cost-neutrality over the cohort’s lifetime.

CONCLUSIONS

When selecting a bisphosphonate for the treatment of high-risk PMO patients, MCOs may realize cost savings and better health outcomes with the use of risedronate (Actonel®) over alendronate (Fosamax®). When treatment effects on chronic disability are considered over the patient’s lifetime, three years of risedronate treatment, compared with no therapy, may produce cost-neutral results.

DISCLOSURE

This study was funded by the Alliance for Better Bone Health, Procter & Gamble Pharmaceuticals, and Aventis Pharmaceuticals. The authors retained control over all data selection, methodology, and interpretation decisions.

REFERENCES