Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis

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Abstract

Introduction: Risedronate has been shown to be effective in the treatment of postmenopausal osteoporosis when given orally in daily or weekly doses or on 2 consecutive days per month. This randomized, double-blind, multi-center study was designed to assess the efficacy and safety of a single 150 mg risedronate once-a-month oral dose compared with the 5 mg daily regimen.

Methods: Women with postmenopausal osteoporosis were randomly assigned to receive risedronate 5 mg daily (n = 642) or 150 mg once a month (followed by daily placebo) (n = 650) in a double-blind fashion for 2 years. Study drug was taken on an empty stomach at least 30 min before breakfast. Bone mineral density, bone turnover markers, fractures, and adverse events were evaluated. The primary efficacy endpoint was the mean percent change from baseline in lumbar spine bone mineral density after 1 year.

Results: 538 patients in the daily group (83.8%) and 556 patients in the once-a-month group (85.5%) completed 1 year. The mean percent change in lumbar spine bone mineral density was 3.4% (95% confidence interval, 3.03% to 3.82%) in the daily group and 3.5% (95% confidence interval, 3.15% to 3.93%) in the once-a-month group. The difference between groups was −0.1% (95% confidence interval, −0.51% to 0.27%). The once-a-month regimen was determined to be non-inferior to the daily regimen based on prospectively defined criteria. The mean percent changes in bone mineral density at sites in the hip (total proximal femur, femoral neck, femoral trochanter) were also similar in both dose groups, as were the changes in biochemical markers of bone turnover. The incidence of adverse events, adverse events leading to withdrawal, and upper gastrointestinal tract adverse events were similar in the 2 treatment groups. Both regimens were well tolerated; the percent of patients who withdrew from treatment as a result of an adverse event was 9.5% in the daily group and 8.6% in the once-a-month group.

Conclusions: Risedronate 150 mg once a month is similar in efficacy and safety to daily dosing and may provide an alternative for patients who prefer once-a-month oral dosing.

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Keywords: Bone mineral density; Fracture risk; Monthly; Osteoporosis; Risedronate

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Introduction

Risedronate is a pyridinyl bisphosphonate that has been shown in prospective fracture studies to reduce vertebral and nonvertebral fracture risks [1–3] and is widely used in the treatment of postmenopausal osteoporosis. Like other bisphosphonates, risedronate remains active on the surface of bone for long periods after dosing, providing the opportunity to develop a range of dosing schedules.

Although the original dosing regimen for postmenopausal osteoporosis was an oral dose of 5 mg risedronate daily [1–3], it was later demonstrated that 35 mg once a week provided similar efficacy and safety to the daily regimen [4]. Risedronate 75 mg each day for 2 consecutive days a month has also been shown to be effective and was recently approved by the Food and Drug Administration for the treatment and prevention of postmenopausal osteoporosis [5,6]. The current randomized, double-blind, 2-year study was undertaken to determine whether a single risedronate dose of 150 mg once a month provides efficacy and safety similar to the 5 mg daily regimen in women with postmenopausal osteoporosis. The primary efficacy analysis was the test of the non-inferiority of the mean percent change from baseline in lumbar spine bone mineral density (BMD) in the risedronate 150 mg once-a-month dose group compared with the 5 mg daily dose group after 1 year. This manuscript reports the efficacy and safety results for the first year of the study, which is continuing for a second year.

Materials and methods

Study design

This randomized, double-blind, active-controlled, parallel-group study was conducted at 47 study centers in the Americas, Europe, Australia, and Asia. The first patient was screened in October, 2005 and the last patient observation for the first year of the study took place in March, 2007. The study was performed in accordance with good clinical practice and the ethical principles that have their origin in the Declaration of Helsinki. The protocol was approved by the appropriate institutional review boards or ethics committees and the patients gave written, informed consent to participate.

Patients

Women were eligible to enroll in the study if they were at least 50 years of age, ambulatory, in generally good health, postmenopausal (at least 5 years since last menses), had at least 3 vertebral bodies in the lumbar spine (L1 to L4) that were evaluable by densitometry (i.e., without fracture or degenerative disease), and had a lumbar spine BMD corresponding to a T-score of $<-2.5$ or a T-score of $<-2.0$ with at least one prevalent vertebral fracture (T4 to L4). Exclusion criteria included any previous or ongoing condition that the investigator judged could prevent the patient from being able to complete the study, drug or alcohol abuse, conditions that would interfere with the BMD measurements, bilateral hip prostheses, history of cancer in the last 5 years excluding basal or squamous skin cancers or successfully treated cervical cancer in situ, body mass index greater than 32 kg/m², allergy to bisphosphonates, use of medications that could interfere with the study evaluations (e.g., glucocorticosteroids, anabolic steroids, estrogens, selective estrogen receptor modulators, calcitonin, any bisphosphonates, fluoride, strontium, PTH), abnormal clinical laboratory measurements, creatinine clearance less than 30 ml/min, hypo- or hypercalcemia, history of hyperparathyroidism or hyperthyroidism unless corrected, osteomalacia, and lumbar spine BMD corresponding to a T-score of $<-5$ or lower. Eligible patients who gave consent were randomly assigned in a 1:1 ratio to the 2 treatment groups.

Treatments

Patients received oral risedronate 5 mg daily or 150 mg once a month (i.e., a single 150 mg tablet on the same calendar day each month, followed by a placebo tablet daily for the rest of the month). The choice of 150 mg as the appropriate monthly dose was based upon a previous, Phase II dose-ranging study [7]. All tablets were identical in appearance and supplied in identical blister cards. Tablets were taken on an empty stomach in the morning at least 30 min before the first food or drink of the day, with at least 4 oz. of plain water. Patients were instructed to remain in an upright position for at least 30 min after dosing. Patients were determined to be compliant if they took at least 80% of the study tablets. Calcium (1000 mg/day) and vitamin D (400–500 IU/day) were supplied to all patients. Patients were allowed to take up to 1000 IU/day of vitamin D. Patients were instructed to take these supplements with a meal other than breakfast and not with the study medication, in order to avoid interference with absorption of risedronate.

Efficacy assessments

Dual energy X-ray absorptiometry (DXA) measurements of lumbar spine and proximal femur were obtained at baseline and after 6 and 12 months using instruments manufactured by Lunar Corporation (General Electric, Madison, WI, USA) or Hologic (Waltham, MA, USA). DXA scans collected at the clinical sites were sent to a central facility for quality control and analysis. Instrument quality control was also monitored throughout the study by the central facility (Synarc, Copenhagen/Hamburg).

Vertebral fractures were assessed by semi-quantitative analysis [8] of lateral thoracic and lumbar spine radiographs collected at screening and after 12 months. Radiographs were reviewed for quality and analyzed for fracture at a central site (Synarc, Copenhagen/Hamburg).

Biochemical markers of bone turnover were assessed at 3, 6 and 12 months. Serum bone-specific alkaline phosphatase (BAP) was measured using an immunochemiluminescence assay on an automated analyzer (Ostase, Access, Beckman Coulter, LaBrea, CA) using the Ostase reagent. The intra- and interassay coefficients of variation for this measurement were less than 4% and 10%, respectively. The detection limit of the test was 0.07 ng/ml and the limit of quantitation was 0.28 ng/ml. Urinary type-1 collagen cross-linked N-telopeptide (NTX) was measured with an electrochemiluminescent immunoassay on an automated machine (Vitros ECI, Johnson and Johnson, Rochester, NY) using the NTx Reagent Pack kit (Ortho-Clinical Diagnostics, Rochester, NY). The intra- and interassay coefficients of variation were below 7% and 6%, respectively. The detection limit of the test was 4 nM and the limit of quantitation was 22 nM. This measurement was corrected for creatinine (NTx/Cr). Serum type-1 collagen cross-linked C-telopeptide (CTX) was measured using an enzyme immunoassay kit (Serum CrossLaps®, Nordic Bioscience Diagnostics, Herlev, Denmark). The intra- and interassay coefficients of variation were below 8% and 6%, respectively. The lower limit of detection was 0.044 ng/ml. The results of the bone turnover marker assays were evaluated at a central laboratory (Synarc SAS, Lyon).

Safety assessments

Physical examinations were performed at baseline and after 12 months. Vital signs, concomitant medications, and adverse event reports were recorded at regular clinic visits throughout the study. Blood and urine samples for clinical chemistry and other standard laboratory measurements (e.g., calcium metabolism, hematology, liver and renal function) were collected at baseline and after 3, 6, 9, and 12 months of treatment. While the study was on-going, the protocol was amended so that these measurements were first obtained at 14 days instead of at 3 months. Specimens were analyzed by Quintiles Laboratories (Smyrna, GA, USA).

Statistical analysis

The primary endpoint analysis was a test of non-inferiority comparing the least squares mean percent change from baseline in lumbar spine BMD in the
150 mg once-a-month and 5 mg daily groups after 12 months; this test employed a pre-defined non-inferiority margin of 1.5% and a 1-sided type I error of 2.5%. The Month 12 measurement or the last post-baseline measurement obtained prior to Month 12 was used (last observation carried forward, also referred to as Endpoint). Investigative centers were pooled by geographic region prior to unblinding. An analysis of variance (ANOVA) was performed with treatment and pooled centers as fixed effects and percent change from baseline in lumbar spine BMD as the response variable. Continuous secondary efficacy variables were analyzed using similar ANOVA methods. 95%, 2-sided confidence intervals were constructed for changes from baseline and between treatment groups. Baseline characteristics of the treatment groups were compared using 1-way ANOVA for continuous variables and Fisher’s Exact Test for categorical variables.

**Results**

**Patients**

A total of 2221 women were screened; of these, 1294 patients were randomized, and 1292 patients received at least 1 dose of study drug (Fig. 1). The most common reasons for screen failure were that the patient did not meet BMD or clinical laboratory criteria, or did not consent to participate in the study. Baseline characteristics were similar in both treatment groups (Table 1), except that patients in the once-a-month dose group were 1 year older on average ($p=0.014$) and a higher percentage of patients were more than 10 years past the last menses ($p=0.03$) compared with the daily dose group. A similar percentage of patients in each treatment group completed 12 months of the study (5 mg daily group, 83.8%; 150 mg once-a-month group, 85.5%). The most common reasons given for withdrawal were adverse event and voluntary withdrawal, which occurred at similar incidences in both treatment groups. Voluntary withdrawals were, by definition, unrelated to adverse events, and usually were attributed by the patient to inconvenience or inability to travel to the clinic. A high percentage of patients in both groups (95.0% of patients in the 5 mg daily group and 96.5% of patients in the 150 mg once-a-month group) took at least 80% of the study tablets.

**Efficacy assessments**

The least squares mean percent change (95% confidence interval) from baseline in lumbar spine BMD at Endpoint (Month 12 with the last observation carried forward) was 3.4% (3.03% to 3.82%) in the daily group and 3.5% (3.15% to 3.93%) in the once-a-month group, indicating that both groups experienced significant improvement from baseline in lumbar spine BMD (Fig. 2). The difference between groups (i.e., the change in the daily group minus the change in the once-a-month group) was $-0.1\%$, with a 95% confidence interval of $-0.51\%$ to 0.27%. The upper limit of the confidence interval for the difference between the groups was less than the pre-defined non-inferiority margin of 1.5%. Therefore, the once-a-month regimen was determined to be non-inferior to the daily regimen with respect to changes in lumbar spine bone mineral density. Analysis using a 2-way ANOVA model with fixed effects for treatment, pooled center, and the treatment-by-pooled center interaction was performed to assess the homogeneity of the treatment effect. The treatment-by-pooled center interaction was not significant, indicating that the treatment effect was consistent across geographies. Analysis
Table 1
Summary of baseline characteristics

<table>
<thead>
<tr>
<th>Risedronate</th>
<th>5 mg daily (N=642)</th>
<th>150 mg once a month (N=650)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>64.4 (7.7)</td>
<td>65.4 (7.2)</td>
</tr>
<tr>
<td>Time since menopause (years), mean (SD)</td>
<td>17.3 (8.6)</td>
<td>18.1 (8.2)</td>
</tr>
<tr>
<td>Time since last menses, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 10 years</td>
<td>167 (26.0)</td>
<td>135 (20.8)</td>
</tr>
<tr>
<td>More than 10 years</td>
<td>475 (74.0)</td>
<td>515 (79.2)</td>
</tr>
<tr>
<td>Race/ethnicity, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>607 (94.5)</td>
<td>613 (94.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>34 (5.3)</td>
<td>33 (5.1)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, no. (%)</td>
<td>189 (32.9)*</td>
<td>185 (31.8)*</td>
</tr>
<tr>
<td>Standardized bone BMD (mg/cm²), mean (SD)</td>
<td>752.55 (67.23)</td>
<td>752.23 (68.52)</td>
</tr>
<tr>
<td>Lumbar spine BMD T-score, mean (SD)</td>
<td>-3.18 (0.56)</td>
<td>-3.21 (0.57)</td>
</tr>
<tr>
<td>Standardized total proximal femur BMD (mg/cm²), mean (SD)</td>
<td>733.10 (92.34)</td>
<td>736.30 (98.03)</td>
</tr>
<tr>
<td>Proximal femur BMD T-score, mean (SD)</td>
<td>-1.80 (0.75)</td>
<td>-1.78 (0.80)</td>
</tr>
<tr>
<td>Urinary NTX/Cr (nmol BCE/nmol Cr), mean (SD)</td>
<td>55.510 (28.709)</td>
<td>56.365 (32.226)</td>
</tr>
<tr>
<td>Serum CTX (ng/mL), mean (SD)</td>
<td>0.622 (0.285)</td>
<td>0.623 (0.295)</td>
</tr>
<tr>
<td>Serum BAP (μg/L), mean (SD)</td>
<td>14.872 (5.386)</td>
<td>14.565 (5.434)</td>
</tr>
</tbody>
</table>

BAP = bone-specific alkaline phosphatase, BMD = bone mineral density, CTX = type-1 collagen cross-linked C-telopeptide, NTX = type-1 collagen cross-linked N-telopeptide corrected for creatinine.

* Percent is based upon the number of patients with known vertebral fracture status (5 mg daily group, 574; 150 mg once-a-month group, 582).

b Adjusted to account for machine type.

using an ANCOVA with adjustments for age and years since last menses (the 2 baseline parameters that were different between treatment groups) gave results consistent with the primary analysis. There was no statistically significant difference between the treatment groups in mean percent change in lumbar spine BMD at any time point (i.e., Month 6, Month 12, or Endpoint).

Significant increases from baseline in BMD of sites in the proximal femur (total proximal femur, femoral neck, femoral trochanter) were observed at 6 months and 12 months in both treatment groups (Fig. 2). As was the case for lumbar spine BMD, there was no statistically significant difference between treatment groups at any time point at any hip site.

There was no difference between treatment groups in the occurrence of new incident vertebral fracture as determined by morphometric measurement during the first 12 months of treatment: 8 patients in each treatment group experienced such a fracture.

Significant decreases from baseline in NTX/Cr, CTX, and BAP were observed at 3, 6 and 12 months in both treatment groups (Fig. 3). In general, changes from baseline in these biochemical markers were similar in both treatment groups. Statistically significant differences between treatment groups were seen at isolated time points, particularly for CTX. There was no statistically significant difference between treatment groups at Endpoint (the last-observation-carried forward values at Month 12) for any of the biochemical markers of bone turnover.

Safety assessments

Overall, the adverse event profile was similar in both treatment groups during the first 12 months of treatment (Table 2). Among the most common adverse events, only diarrhea and influenza were substantially more common in the monthly group compared with the daily group (Table 2). Most events of diarrhea were mild or moderate in severity. Five patients (0.8%) in the 150 mg once-a-month group and no patient in the 5 mg daily group withdrew from the study as a result of diarrhea. Most cases of influenza occurred more than 90 days after the start of treatment. All events of influenza were mild or moderate in severity and none of the patients withdrew because of influenza.

Adverse events of special interest for bisphosphonates (clinical vertebral and nonvertebral fractures, upper gastrointestinal tract adverse events, and musculoskeletal adverse events) were reported by similar proportions of patients in both treatment groups (Table 2). The incidence of symptoms potentially associated with an acute phase reaction (influenza-like illness and/or pyrexia starting within 3 days following the first dose of study drug and having a duration of 7 days or less), although low in both groups, was slightly higher in the monthly group (1.4%) than in the daily group (0.2%) (Table 2). Most events associated with possible acute phase reactions were determined by the investigator to be mild or moderate in severity; only 1 patient, in the once-a-month group, experienced an event that was severe. Atrial fibrillation was reported by 3 patients (0.5%) in the 5 mg daily group and 4 patients (0.6%) in the 150 mg once-a-month group. There were no reported cases of osteonecrosis of the jaw. In general, results of clinical chemistry and other laboratory measurements, including measures of hepatic and renal function, were similar in both treatment groups.

Discussion

Risedronate is a widely used osteoporosis treatment with proven vertebral and nonvertebral antifracture efficacy and a minimum wait of 30 min after dosing before eating or drinking anything other than water. A 5-mg daily regimen was developed originally, but less frequent dose regimens have now been developed. This study found that risedronate 150 mg once a month produces clinical effects that are similar to those seen with the 5 mg daily dose regimen. Specifically, the mean percent change in lumbar spine BMD at 12 months in the monthly group was non-inferior to the mean percent change in the daily group. Changes in secondary efficacy parameters, including BMD at the hip, bone turnover markers at endpoint, and morphometric vertebral fractures, were also similar in both groups and both regimens had similar safety profiles. Statistically significant differences...
between treatment groups were observed for all 3 bone turnover markers at Month 3, but persisted at Months 6 and 12 for CTX only; no statistically significant differences between groups were observed for any marker at Endpoint. Although statistically significant differences between groups were seen at some time points, these differences should be considered in light of differences between the two regimens in the kinetics of bone resorption suppression. One might expect the monthly regimen to produce a larger initial decrease in bone resorption during the first week after dosing than that seen with daily dosing. This decrease would then be followed by a gradual and mild increase, reaching an overall level of suppression before the next dose that is only slightly less than that achieved with daily dosing. The observed differences between groups in bone turnover markers are not considered to be clinically meaningful.

The results of this study are consistent with previous studies of less frequent dosing that showed the treatment effects of risedronate 35 mg weekly and 75 mg on 2 consecutive days each month were similar to the effects of daily dosing [4–6] and that the bisphosphonate ibandronate can be dosed on a monthly basis [9]. These various dosing options, including the ability to dose at widely spaced intervals, are a result of the ability of bisphosphonates to adhere to bone and exert sustained effects on bone metabolism.

This study found that the risedronate 150 mg once-a-month dose was generally well tolerated by postmenopausal women, with a safety profile similar to that seen with the 5 mg daily regimen. This finding is consistent with the results of studies in Paget’s disease that have demonstrated a favorable safety profile even with dosing of 30 mg risedronate daily for
2 months [10] or longer [11]. Although symptoms associated with potential acute phase reaction (influenza-like symptoms and/or pyrexia) occurred more frequently in the once-a-month dose group than in the daily dose group in this study, the incidence was low in both treatment groups and all but 1 of these events were mild or moderate in severity. Of 9 subjects in the once-a-month group who experienced these reactions, only 1 discontinued treatment as a result. This observation suggests that the increased incidence of these reactions with the once-a-month regimen will have a minimal impact on adherence to treatment in clinical use. A similar reaction has been seen in other studies of oral bisphosphonates. The percentage of patients reporting fever or influenza-like illness within 5 days of treatment was increased with oral risedronate 75 mg each day on 2 consecutive days each month when compared with 5 mg daily dosing (0.6% vs. 0%) [5]. Similarly, the incidence of influenza-like illness and acute phase reaction was increased in patients receiving oral ibandronate 150 mg once a month when compared with 2.5 mg daily (3.3% vs. 0.8%) [12]. Acute phase reactions have been reported at higher incidence during treatment with intravenous N-containing bisphosphonates including, most recently, zoledronic acid [13–16]. In a placebo-controlled study of a once-yearly infusion, 31.6% of patients in the zoledronic acid group reported pyrexia, myalgia, influenza-like symptoms, headache, or arthralgia within the first 3 days after the first infusion, compared with 6.2% of placebo patients. The incidence declined with subsequent infusions [16]. BMD change is an appropriate endpoint when evaluating a new dosing schedule of a bisphosphonate for which a fracture benefit has already been established. Similar non-inferiority trials have been conducted previously to evaluate new dosing regimens of oral bisphosphonates [4,17] and this approach has been accepted by both the U.S. Food and Drug Administration and the EMEA [18] for approval of new regimens of established agents. The magnitude of BMD change associated with the vertebral and nonvertebral antifracture efficacy of risedronate has been established in

![Graph](image-url)

Fig. 3. Mean percent change from baseline in biochemical markers of bone turnover over 1 year in women receiving risedronate 5 mg daily or 150 mg once a month. Urinary NTX/creatinine (left panel), serum CTX (center panel), serum BAP (right panel). Endpoint refers to the value calculated using the last observation carried forward at Month 12. The asterisk (*) indicates a statistically significant difference between treatment groups (p<0.05, unadjusted for multiple comparisons).

Table 2

<table>
<thead>
<tr>
<th>Summary of adverse events</th>
<th>Risedronate 5 mg daily (N=642), n (%)</th>
<th>150 mg once a month (N=650), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>504 (78.5)</td>
<td>515 (79.2)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>27 (4.2)</td>
<td>40 (6.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>3 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawn due to an adverse event*</td>
<td>61 (9.5)</td>
<td>56 (8.6)</td>
</tr>
<tr>
<td>Most common adverse event associated with withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>36 (5.6)</td>
<td>38 (5.8)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>39 (6.1)</td>
<td>53 (8.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30 (4.7)</td>
<td>53 (8.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>47 (7.3)</td>
<td>38 (5.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>27 (4.2)</td>
<td>58 (8.9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>47 (7.3)</td>
<td>36 (5.5)</td>
</tr>
<tr>
<td>Adverse events of special interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical vertebral fracture</td>
<td>4 (0.6)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Nonvertebral fracture</td>
<td>18 (2.8)</td>
<td>13 (2.0)</td>
</tr>
<tr>
<td>Upper gastrointestinal tract adverse event</td>
<td>110 (17.1)</td>
<td>129 (19.8)</td>
</tr>
<tr>
<td>Selected musculoskeletal adverse events*</td>
<td>110 (17.1)</td>
<td>101 (15.5)</td>
</tr>
<tr>
<td>Adverse events potentially associated with acute phase reaction*</td>
<td>1 (0.2)</td>
<td>9 (1.4)</td>
</tr>
</tbody>
</table>
multiple large studies that had fracture as the primary endpoint [1–3]. Although current data for the oral risedronate 150 mg once-a-month dose are limited to 1 year’s treatment duration, the study is being continued for another year to assess the effects of longer-term treatment. In previous clinical trials, patients receiving the risedronate 5 mg daily regimen have been followed in clinical trials for up to 7 years, with no evidence of loss of effectiveness [19].

In this study, the risedronate 150 mg once-a-month dosing regimen was comparable in safety and efficacy to daily dosing in the treatment of postmenopausal osteoporosis. The addition of this dosing regimen to the therapeutic armamentarium will provide osteoporosis patients with a full range of risedronate dosing options, from daily to weekly to monthly, with the benefits of proven vertebral and non-vertebral fracture efficacy and a minimum 30-min wait before eating.

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Appendix A


References