Denosumab (Prolia) Injection

A New Approach to the Treatment of Women With Postmenopausal Osteoporosis

Wendy Green, PharmD, MPA

INTRODUCTION

A healthy skeleton is essential for providing structural support, protection of vital organs and the hematopoietic system, and maintenance of homeostasis of calcium and other ions. Skeletal bone (composed of trabecular and cortical bone) is a dynamic tissue that constantly undergoes remodeling in response to mechanical stresses and hormonal changes.1–3 This constant remodeling is a dichotomous process, essential in repairing microdamage and renewing skeletal integrity and strength.4 Osteoblasts, osteocytes, and osteoclasts serve as key components in this parallel physiological pathway to support remodeling. Osteoblasts (which form bone lining) and osteocytes (osteoblasts that form bone matrix and transmit signals) have functions dissimilar those of osteoclasts, which break down bone. Osteoblasts and osteocytes are analogous to "building blocks" of the skeletal system because they are involved in bone formation, contrary to osteoclast-inhibiting activity, which leads to bone resorption.

Systemic and local regulators of bone cell activity control resorption and formation; hence, these two processes are intimately intertwined. Bone resorption and bone formation are continual, and this method of remodeling replaces the entire human skeleton every decade.4 In bone metabolism, a cascade of biochemical reactions facilitates bone remodeling, including the human receptor activator of nuclear factor-κB (RANK) and RANK ligand (RANKL) succession, of which osteoblasts and osteoclasts are essential local regulators. Osteoblasts regulate osteoclastic formation and activity by secreting RANK or osteoprotegerin (OPG). RANK provides the osteoblast a pathway to stimulate formation of mature osteoclasts (increased bone resorption) whereas OPG secretion promotes inhibition of mature osteoclasts (decreased bone resorption).

Under normal circumstances, bone resorption in adults is equivalent to bone formation and represents no net loss or gain in bone mass.5 When the process of remodeling favors resorption over formation, an imbalance in activity is created and osteoporosis may occur. Osteoporosis is characterized by low bone mass and microstructural deterioration of bone tissue, leading to increased fragility and fractures. Many modifiable and nonmodifiable factors are associated with an increased risk of osteoporosis and related bone fractures; however, the key risk factors most often associated with clinical fractures are low bone mass and falls (Table 1).5,7 Although bone resorption and formation are the focal points of this discussion, other steps involved in bone remodeling include reversal and quiescence as well as an array of cytokine and hormonal activities.5,8

The Office of the Surgeon General and the Third National Health and Nutritional Examination Survey (NHANES III, 1988–1994) have provided important data on osteoporosis.3,6 Complementary epidemiologic studies suggest that 10 million Americans have osteoporosis and another 34 million Americans 50 years of age and older are at risk.5 The Office of the Surgeon General’s report on bone health and osteoporosis in 2004 stated that 50% of women 50 years of age and older would have an osteoporotic-related fracture in their lifetime, with the risk of fracture increasing with age.5 The Surgeon General also estimated that the aging of the population in the U.S., coupled with the previous lack of focus on bone health, could result in doubling or tripling the number of hip fractures by 2020.3

NHANES III retrospective data also indicate that osteoporosis is the most common and preventable bone disease, with non-Hispanic Caucasian women having the highest prevalence of osteopenia and osteoporosis, among Americans; the prevalence of osteoporosis is even higher among nursing-home residents.10 To bolster support for and promote the importance of bone health and preventing fractures, former President George W. Bush declared the years 2002 to 2011 as the “Bone and Joint Decade,”11 part of the objectives for the Healthy People 201012 and the proposed objectives for Healthy People 202013 initiatives.

Several organizations have developed guidelines for the diagnosis and management of osteoporosis, such as the World Health Organization (WHO), the European Foundation for Osteoporosis, and the National Osteoporosis Foundation WHO uses the T-score—the number of standard deviations (SDs) from the mean, compared with average bone mass of healthy young women—as a measurement to classify bone mass or bone mineral density (BMD). T-scores assist health care professionals in establishing the degree of bone health, assessing fracture risk, and steering prevention and treatment decisions. Diagnostic testing, however, has been reserved for use in postmenopausal women and men 50 years of age or older.4 Normal BMD is a T-score greater than –1.0 SD; osteoporosis is defined as a T-score of less than –2.5 SD.6

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The armamentarium of pharmacological agents used in the effort to prevent and treat osteoporosis is expanding in terms of mechanisms of action as well as in the frequency and routes of administration. To this end, the FDA has granted approval to Amgen for its first RANK ligand inhibitor, denosumab (Prolia). Inhibition of turnover at this level of bone metabolism is a novel approach in preventing and managing osteoporosis, with many implications.

**INDICATION AND USAGE**

Denosumab, a RANK ligand (RANKL) inhibitor, is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Patients considered to be at a high risk are those who have a history of an osteoporotic fracture, have multiple risk factors for fracture, or have not responded to, or who are intolerant of, other available osteoporosis therapies. In postmenopausal women with osteoporosis, denosumab has been noted to reduce the incidence of vertebral, nonvertebral, and hip fractures.

**CLINICAL PHARMACOLOGY**

Denosumab is a human immunoglobulin G2 (IG2) monoclonal antibody genetically engineered in Chinese hamster ovarian (CHO) cells. The drug’s approximate molecular weight is 147 kDa. Denosumab inhibits the receptor activator of nuclear factor-κB ligand (RANKL) and the receptor activator of nuclear factor-κB (RANK) complex (Figure 1). This RANKL–RANK complex is essential in osteoclast-mediated bone resorption. Inhibition of this complex reduces bone turnover and resorption, thereby increasing bone mass and strengthening cortical and trabecular bone.

**PHARMACOKINETIC AND PHARMACODYNAMICS**

After a fast of 12 hours, a single subcutaneous (SQ) administration of 60 mg of denosumab in healthy males and females resulted in a peak concentration (C\text{max}) and a time to peak concentration (T\text{max}) of 6.75 mcg/mL (±1.89 mcg/mL) and 10 days (range, 3–21 days), respectively. Serum concentrations declined over a period of four to five months, with a half-life of 25.8 days (SD = 8.5 days) following the C\text{max}. No accumulation or delta in denosumab pharmacokinetics was observed over time when multiple SQ injections of 60-mg doses were administered every six months in healthy subjects. Moreover, the drug’s pharmacokinetic properties were not affected by binding antibodies, age (postmenopausal women), sex, race, or body weight in

![Figure 1](https://example.com/figure1.png)

**Table 1 Risk Factors Affecting Bone Health**

<table>
<thead>
<tr>
<th>Factors Associated With Fracture Risk</th>
<th>Factors Associated With Low Bone Mass</th>
<th>Factors Associated With Falls</th>
</tr>
</thead>
<tbody>
<tr>
<td>• BMD at the femoral neck</td>
<td>• Sex (female)</td>
<td>• Prior fall or fear of falling</td>
</tr>
<tr>
<td>• Low BMI</td>
<td>• Ethnicity (Caucasian or Asian)</td>
<td>• Impaired senses</td>
</tr>
<tr>
<td>• Prior fragility fracture</td>
<td>• Lifestyle (sedentary)</td>
<td>• Physical disabilities</td>
</tr>
<tr>
<td>• Glucocorticoid exposure</td>
<td>• Immobility</td>
<td>• Environmental obstacles and hazards</td>
</tr>
<tr>
<td>• Parenteral history of (hip) fracture</td>
<td>• Low body weight (&lt;125 pounds)</td>
<td>• Orthostatic hypotension</td>
</tr>
<tr>
<td>• Smoking</td>
<td>• Low calcium intake (anytime in life)</td>
<td>• Visual impairment</td>
</tr>
<tr>
<td>• Excessive intake of alcohol</td>
<td>• Weight loss (&gt;10% of weight at age 25)</td>
<td>• Cognitive impairment</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td>• Malnutrition</td>
<td>• Medications (i.e., BZD, TCA, hypotensive agents)</td>
</tr>
</tbody>
</table>

BMD = bone mineral density; BMI = body mass index; BZD = benzodiazepine; TCA = tricyclic antidepressant.

(Rankin P. Curr Osteoporos Rep 2009;7:18–22, with permission from Springer.)
patients weighing 36 to 140 kg (about 79 to 308 pounds). No dosage adjustments are recommended for patients with renal or hepatic impairment on the basis of pharmacokinetic studies.

A serum type 1 C-telopeptide (CTX) was a marker used to measure reductions in bone resorption. After three days of treatment with denosumab 60 mg, there was an 85% reduction in CTX, with maximal reductions occurring by one month. After one to three months, 39% to 68% of subjects had CTX levels below assay limits (0.049 ng/mL). Denosumab and CTX levels have an inverse relationship, demonstrating the reversibility of denosumab’s effects.

**CLINICAL TRIALS**

To date, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every Six Months (FREEDOM) and the Study of Transitioning from Alendronate to Denosumab (STAND) are the clinical trials that helped to gain the FDA’s approval of denosumab. Other trials are currently evaluating denosumab against placebo, alendronate (Fosamax, Merck), or both, but FREEDOM and STAND, independently, have enrolled the most participants thus far.

**McClung et al.**

In this randomized, dose-ranging, placebo-controlled trial, investigators sought to determine the efficacy and safety of SQ denosumab given over a period of 12 months. Study participants received blinded denosumab injections every three months or every six months, open-label alendronate, or placebo and were evaluated for one year (Table 2). The trial enrolled 412 postmenopausal women, up to 80 years of age (mean age, 63 years). T-scores ranged from –1.8 to –4.0 at the lumbar spine and from –1.8 to –3.5 at the femoral neck or total hip. The primary endpoint was the percentage of change in T-scores at the lumbar spine at 24 months.

Results for both strata were similar; denosumab significantly increased lumbar spine BMD, compared with placebo at 24 months (6.5% vs. –0.6%, respectively). Overall, twice-yearly denosumab therapy increased BMD and decreased bone turnover markers in both early and late postmenopausal women.

**Bone et al.**

A two-year, placebo-controlled, double-blind phase 3 trial was conducted in 332 postmenopausal women to evaluate the ability of denosumab to increase BMD and decreased markers of bone turnover. Lumbar spine T-scores ranged from –1.0 to –2.5.

To be enrolled, in addition to being postmenopausal and having substantial BMD T-scores, subjects needed to meet the following criteria:

- a history of oral bisphosphonate therapy of less than three months or a 12-month washout period if cumulative bisphosphonate therapy was between three months and three years
- ability to be ambulatory
- absence of medications affecting bone metabolism other than calcium and vitamin D supplements
- no other underlying condition that might have resulted in abnormal bone metabolism
- no history of a fracture after age 25

Subjects received SQ injections of denosumab 60 mg or placebo every six months. Randomization was stratified by the time since the onset of menopause (less than or more than five years). Although markers for bone turnover were assessed, the primary endpoint was the percentage of change in T-scores at the lumbar spine at 24 months.

Results for both strata were similar; denosumab significantly increased lumbar spine BMD, compared with placebo at 24 months (6.5% vs. –0.6%, respectively). Overall, twice-yearly denosumab therapy increased BMD and decreased bone turnover markers in both early and late postmenopausal women.

**Kendler et al.**

STAND was a one-year international, phase 3, multicenter, double-blind, double-dummy, parallel-group, randomized controlled trial (n = 504), conducted between October 2006 and March 2008. Randomization was stratified by prior duration of alendronate treatment as follows: 6 to less than 12 months, 12 to 24 months, and more than 24 months. The aim of this study was to evaluate the impact on safety, BMD, and bone remodeling in patients switching from alendronate to denosumab. The primary efficacy endpoint was the percentage change from baseline in total hip BMD at 12 months; secondary efficacy endpoints included percentage change from baseline in serum CTX levels and lumbar spine at 3 and 12 months, respectively.

Eligible women were postmenopausal and at least 55 years of age with T-scores between –2.0 and –4.0 at the lumbar spine or total hip and had a minimum six-month history with alendronate treatment equivalent to 70 mg/week. All subjects received oral alendronate 70 mg once weekly during a one-month run-in period. Subjects subsequently received SQ denosumab 60 mg every six months or oral alendronate 70 mg once weekly for 12 months, with corresponding placebo injections or tablets.

Baseline characteristics were similar for age and BMI in both treatment groups. The average duration of alendronate use immediately preceding screening for all subjects was 36 months, with a range of 6 to 192 months (0.5–16 years). T-scores for total hip and lumbar spine were similar for both groups, averaging –1.8 and –2.63, respectively, with previous osteoporosis-related fracture in 50% of women. Study results showed an increase in T-scores with both denosumab (1.9%; 95% confidence interval

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**Table 2 Stratification of Treatment Groups in a Dose-Ranging Study**

<table>
<thead>
<tr>
<th>Placebo (n = 46)</th>
<th>Denosumab:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Injection every 3 months: 6 mg¹, 14 mg², and 30 mg³ (n=127)</td>
</tr>
<tr>
<td></td>
<td>Injection every 6 months: 14 mg⁴, 60 mg⁵, 100 mg⁶, and 210 mg⁷ (n=187)</td>
</tr>
<tr>
<td>Alendronate:</td>
<td>70 mg once weekly (n = 46)</td>
</tr>
</tbody>
</table>

¹ n = 43; ² n = 44; ³ n = 40; ⁴ n = 53; ⁵ n = 47; ⁶ n = 41; ⁷ n = 46.

Data from McClung.¹⁴
Cummings et al. ⁸

In FREEDOM, an international, randomized controlled trial, patients received SQ injections of either denosumab 60 mg or placebo every six months for 36 months. Spine radiographs were assessed annually to determine efficacy. The investigators enrolled 7,868 subjects; considering both groups, 84.7% were enrolled in Western (n = 3,534) and Eastern European regions (n = 3,128). Baseline characteristics were similar among both groups; mean age and body mass index (BMI) were 72.3 years (±5.2 for both groups) and 26 (±4.1 and 4.2 for denosumab and placebo, respectively).

The aim of this study was to evaluate the effect of denosumab on fracture risk in postmenopausal women with osteoporosis. The primary endpoint was new vertebral fracture at 36 months, with nonvertebral and hip fractures included as secondary endpoints. Randomization was stratified by five-year age groups. Among the many inclusion criteria, the women had to have a T-score between −2.5 and −4.0 at the lumbar spine or total hip, and they had to be between 60 and 90 years of age. Baseline T-scores for the lumbar spine, total hip, and femoral neck were −2.8, −1.9, and −2.2, respectively. Approximately 24% of subjects had a baseline vertebral fracture.

The incidence of new radiographic vertebral fractures and the time to the first nonvertebral and hip fractures with denosumab at 36 months were 2.3%, 6.5%, and 0.7%, respectively, compared with 7.2%, 8%, and 1.2% with placebo, respectively. The associated relative risks were 0.32 (95% CI, 0.26–0.41; P < 0.001), 0.8 (95% CI, 0.67–0.95; P = 0.01), and 0.6 (95% CI, 0.37–0.97; P = 0.04) for vertebral, nonvertebral, and hip fractures, respectively, with resultant risk reductions (RRs) of 68%, 20%, and 40% in vertebral, nonvertebral, and hip fractures, respectively. Although the RR associated with denosumab therapy for vertebral fractures was 68%, this represents a cumulative reduction throughout each trial year, with the highest to lowest RR occurring at 13 to 24 months (78%), followed by 25 to 36 months (65%) and by 0 to 12 months (61%).

A substudy analysis compared BMD results of denosumab and placebo at the lumbar spine and total hip (n = 441), and bone turnover markers (for bone resorption) (n = 160), such as CTX and procollagen type 1 N-terminal pro-peptide. Denosumab was associated with an increase in BMD at the lumbar spine and total hip in 9.2% and 6% of patients, respectively. Compared with placebo, denosumab decreased serum levels of CTX in 86% of patients at one month, in 72% at the pre-six month dose, and in 72% at 36 months.

ADVERSE DRUG REACTIONS

After a 24-month study duration, Lewiecki et al. ¹⁷ found no significant differences in most adverse drug events (ADEs) recorded for denosumab, alendronate, or placebo. The most common ADE was upper respiratory tract infection with denosumab (24.2%), compared with rates of 17.4% for placebo and 23.9% for alendronate. Dyspepsia, arthralgia, and nausea occurred with greater than 20% frequency with all of the treatments. The frequency of dyspepsia was highest with alendronate (26.1%), compared with placebo (6.5%) and denosumab (10.5%). Arthralgia occurred most often with placebo (28.3%), compared with denosumab (19.1%) and alendronate (10.9%).

The number of patients reporting serious ADEs was greatest in the denosumab group (13.4%), followed by alendronate (13%) and placebo (8.7%). Neoplasms (benign and malignant) were the only serious ADEs, occurring in 2% or fewer of the denosumab patients (3.2%).

In the 12-month study of McClung et al., ¹⁸ the most common ADEs, occurring at a frequency of 10% or more for all combined denosumab groups, were upper respiratory tract infection (19.4%), arthralgia (15%), nasopharyngitis (14.6%), and back pain (11.5%). In a comparison of placebo, denosumab 60 mg (only), and alendronate groups, many other ADEs occurred throughout the body at a frequency of 10% or more (Table 3). ¹⁵ For two women receiving denosumab 100 mg every six months, denosumab-binding antibodies were detected, in one patient at one month and in the other patient at 12 months. Further analysis revealed these antibodies to be non-neutralizing.

The safety profile of denosumab, according to Kendler et al., ¹⁴ showed no statistically significant differences in the total incidence of ADEs, serious ADEs, or discontinuation of study treatment between denosumab and placebo. The most commonly reported ADEs with denosumab were back, extremity, and musculoskeletal pain; hypercholesterolemia; and cystitis.

Breast cancer, back pain, and constipation were the most common adverse drug reactions leading to discontinuation of therapy. ¹³ The incidence of serious ADEs, death, withdrawal, and clinical fracture in the denosumab group was similar to that seen with alendronate and placebo, except for serious ADEs (Table 4). ¹⁴

PREGNANCY ¹³

Denosumab is a Pregnancy Category C drug, with effects on both fetal and maternal metabolism in genetically engineered mice. When the RANKL gene was removed, fetal lymph node agenesis and postnatal impairment of dentition and bone growth occurred in its absence. These same mice also showed altered maturation of the maternal mammary gland, leading to impaired postpartum lactation.

DRUG INTERACTIONS ¹³

So far, no drug interactions have been documented. Drug–drug interaction trials have not been conducted to investigate possible interactions between RANKL inhibitors and other pharmacological agents.

PRECAUTIONS AND CONTRAINDICATIONS ¹³,¹⁴,¹⁸–²²

Hypocalcemia

Denosumab may further exacerbate hypocalcemia in patients with pre-existing hypocalcemia and in those individuals predisposed to hypocalcemia. In these circumstances, serum calcium levels must be corrected before denosumab...
is initiated. Patients with imbalances in mineral metabolism (i.e., severe renal impairment, malabsorption syndromes, bowel disease, a history of hypoparathyroidism) should be closely monitored to maintain appropriate serum calcium, phosphorus, and magnesium levels.

### Serious Infections

According to Cummings et al., infections associated with denosumab occurred at a higher rate than with placebo. By comparison, the infections occurring most frequently were not statistically significant, except for cellulitis. The suggested mechanism of the increased risk of infection may be attributable to RANKL inhibition, because RANKL can be found on T and B lymphocytes and in lymph nodes. Therefore, patients taking immunosuppressant agents or patients with impaired immune systems may be at a higher risk for infections, including serious infections.

### Dermatological Adverse Reactions

In some clinical trials, skin infections were observed. Cummings et al. reported the frequency of eczema at 3% with denosumab and at 1.7% with placebo. There was a statistically significant difference in the incidence of cellulitis, including erysipelas, with denosumab (0.3%) when compared with placebo (0.1%). Treatment should be discontinued if skin and skin-structure reactions progress in severity.

### Osteonecrosis of the Jaw

According to reports received by Amgen, jaw osteonecrosis (ONJ) occurred in some patients receiving denosumab. In patients with ONJ, exposed bone in the mouth fails to heal over a period of six to eight weeks after appropriate intervention. The syndrome of ONJ can develop spontaneously. Tooth extraction commonly precipitates ONJ in those patients with risk factors such as prior bisphosphonate therapy, breast or prostate cancer, and myeloma. Monitoring for risk factors, routine oral examinations, and good oral hygiene can help lessen the occurrence of this ADE.

### DOSAGE AND ADMINISTRATION

Denosumab 60 mg is given as a subcutaneous injection by a health care professional once every six months in the patient’s upper arm, upper thigh, or abdomen. Any missed dose should be administered when feasible, and the dosing regimen should be restarted every six months thereafter. Adjunctive therapy with calcium 1,000 mg daily and at least 400 IU daily is also recommended.

The product comes in two package sizes, a prefilled syringe and a single-dose vial. The prefilled syringe comes with an attached needle secured by rubber cap, along with a safety guard to prevent needle recapping. Because the rubber cap is a latex derivative, people with latex allergy or sensitivity should not manipulate the cap.

### COST

Denosumab is available as a 1-mL, 60-mg/mL solution injection (syringe or vial), which is equivalent to one dose every six months. The average wholesale price for the 60-mg prefilled syringe is $990, or $5.50 per day during a six-month treatment period. The cost varies, depending on the wholesaler, institution, or organization and whether the drug is obtained in a clinic setting, at a retail

### Table 3 Any Adverse Events Occurring at a Rate of 10% or More Within Selected Treatment Groups

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 46) Percent (No.)</th>
<th>Denosumab (n = 47)* Percent (No.)</th>
<th>Alendronate (n = 46) Percent (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>13.0% (6)</td>
<td>21.3% (10)</td>
<td>17.4% (8)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>23.9% (11)</td>
<td>8.5% (4)</td>
<td>6.5% (3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13.0% (6)</td>
<td>14.9% (7)</td>
<td>10.9% (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>13.0% (6)</td>
<td>6.4% (3)</td>
<td>10.9% (5)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>8.7% (4)</td>
<td>10.6% (5)</td>
<td>10.9% (5)</td>
</tr>
<tr>
<td>Influenza</td>
<td>2.2% (1)</td>
<td>19.1% (9)</td>
<td>6.5% (3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0.0% (0)</td>
<td>10.6% (5)</td>
<td>6.5% (3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6.5% (3)</td>
<td>6.4% (3)</td>
<td>26.1% (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.3% (2)</td>
<td>8.5% (4)</td>
<td>17.4% (8)</td>
</tr>
</tbody>
</table>

* Only in the denosumab 60-mg treatment group. Data from McClung.

### Table 4 Overall and Serious Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 46) Percent (No.)</th>
<th>Denosumab (n = 314) Percent (No.)</th>
<th>Alendronate (n = 46) Percent (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>89.1% (41)</td>
<td>87.3% (274)</td>
<td>91.3% (42)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>4.3% (2)</td>
<td>5.7% (18)</td>
<td>2.2% (1)</td>
</tr>
<tr>
<td>Death</td>
<td>2.2% (1)</td>
<td>2.2% (7)</td>
<td>0%</td>
</tr>
<tr>
<td>Withdrawal due to an adverse event</td>
<td>2.2% (1)</td>
<td>2.2% (7)</td>
<td>0%</td>
</tr>
<tr>
<td>Clinical fracture</td>
<td>2.2% (1)</td>
<td>3.8% (12)</td>
<td>2.2% (1)</td>
</tr>
</tbody>
</table>

Data from McClung.
**Table 5 Therapy for Osteoporosis and Cost Comparison**

<table>
<thead>
<tr>
<th>Drug</th>
<th>AWP*</th>
<th>Yearly Cost</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate sodium 70-mg tablet; generic tablet (Fosamax)</td>
<td>$20.48 ($24.51)</td>
<td>$1,065 ($1,275)</td>
<td>70 mg orally weekly</td>
</tr>
<tr>
<td>Calcitonin-salmon nasal spray 200 IU/0.09-mL–3.7-mL unit (Fortical)</td>
<td>$102.89</td>
<td>$1,235</td>
<td>200 IU nasally daily</td>
</tr>
<tr>
<td>Risedronate sodium 150-mg tablet (Actonel)</td>
<td>$124.57</td>
<td>$1,495</td>
<td>150 mg orally monthly</td>
</tr>
<tr>
<td>Risedronate sodium 35-mg tablet (Actonel)</td>
<td>$28.75</td>
<td>$1,495</td>
<td>35 mg orally weekly</td>
</tr>
<tr>
<td>Ibandronate sodium 150-mg tablet (Boniva)</td>
<td>$124.66</td>
<td>$1,496</td>
<td>150 mg orally monthly</td>
</tr>
<tr>
<td>Raloxifene HCl 60-mg tablet (Evista)</td>
<td>$4.34</td>
<td>$1,562</td>
<td>60 mg orally daily</td>
</tr>
<tr>
<td>Denosumab 60-mg/mL injection: 1-mL prefilled syringe (Prolia)</td>
<td>$990.00</td>
<td>$1,980</td>
<td>60 mg SQ every 6 months</td>
</tr>
</tbody>
</table>

*AWP = average wholesale price; SQ = subcutaneously.
*From Morris & Dickson, data for outpatient costs.

...drugstore, or by mail order.

The price appears to be comparable to that of many of the oral bisphosphonate and non-bisphosphonate formulations (Table 5). Because self-administration is not advised, according to the manufacturer, the need for a clinician to inject the medication may add to the overall cost of therapy.

**FUTURE STUDIES**

Many old and new agents are quickly emerging for the treatment of osteoporosis. In the ambulatory setting, there are oral and nasal formulations and the new SQ injectable alternative, denosumab. Intravenous administration of pharmacotherapy for osteoporosis is typically reserved for inpatient settings or infusion centers. In addition to the several routes of administration, dosing frequencies may also vary (e.g., daily or weekly).

According to the National Institutes of Health, roughly nine other studies are actively recruiting patients to evaluate the effects of denosumab in additional disease states and patient populations. Some study groups include patients with non-metastatic breast cancer who are taking aromatase inhibitors, men with osteoporosis, patients with malignant hypercalcemia, and patients with non-malignant prostate cancer.

**CONCLUSION**

Denosumab (Prolia) blocks osteoclast-mediated bone resorption by inhibiting RANK and RANKL, thereby decreasing bone turnover and increasing bone mineral density (BMD). Denosumab has been studied in women who are postmenopausal and at high risk for vertebral, nonvertebral, and hip fractures. The FDA’s approval of this drug adds a novel mechanism of action for osteoporosis management compared with current options, and many P&T committees will be eager to evaluate it for addition to the formulary.

This agent also has implications for use in the management of other diseases affected by subsequent bone disease; therefore, establishing criteria for safe, appropriate, and cost-effective use will be imperative as more indications gain approval.

Based on available data and current indications, considerations for useful criteria might include postmenopausal women with persistent total hip, femoral neck, or lumbar spine BMD T-scores ranging from –1.8 to –4.0, despite previous bisphosphonate therapy, for at least six to 12 months, or clinical fracture, even with prior or current bisphosphonate therapy. Although the occurrence of ADEs and serious ADEs is similar with denosumab, placebo, and alendronate, patients should understand safety precautions and methods of monitoring for serious systemic and skin infections in addition to ONJ.

Depending on the average wholesale price at each institution, a cost analysis may show that denosumab is a cost-effective intervention for the treatment of osteoporosis; however, strategies for minimizing denosumab expenditures will be imperative to the judicious use of fiscal resources allocated for pharmacy drug expenses. Moreover, additional outlays could be incurred because the manufacturer’s prescribing information recommends administration by a health care practitioner.

**REFERENCES**


