Prescription Drug Therapies for Prevention and Treatment of Postmenopausal Osteoporosis

MARY BETH O'CONNELL, PharmD, BCPS, FASHP, FCCP

ABSTRACT

OBJECTIVE: To characterize the changes in bone mass with age in women and men, explain the physiology and pathophysiology of the bone remodeling process, identify the targets for prescription osteoporosis drugs in this process, and provide details about the uses, efficacy, safety, and economics of prescription drug therapies for osteoporosis prevention and treatment.

BACKGROUND: Preventing accelerated bone loss and decreasing age-related decreases in bone density are the primary goals of prescription drug therapy for osteoporosis. Bisphosphonates are the drugs of choice for preventing and treating postmenopausal osteoporosis. Alternatives for patients who cannot take bisphosphonates include raloxifene and calcitonin salmon.

SUMMARY: Menopause is accompanied by a rapid loss in bone mass that is followed by annual losses due to aging in women, which are similar to age-related bone mass decreases in men. Most prescription drug therapies for osteoporosis prevention or treatment reduce bone resorption by inhibiting osteoclast activation and activity, with only one medication class able to increase bone formation by stimulating osteoblasts. Denosumab, an investigational monoclonal antibody that inhibits nuclear factor κ B ligand, would be a new class of antiresorptive medications. Bisphosphonates currently are the drugs of choice for preventing and treating osteoporosis, with 7- and 10-year safety data available for risedronate and alendronate, respectively. Weekly and monthly regimens of bisphosphonates improve patient acceptance. Recently, an injectable form of ibandronate received U.S. Food and Drug Administration approval for once every 3 months administration. Raloxifene and calcitonin salmon are alternatives for patients who cannot take bisphosphonates because of contraindications or adverse effects. Teriparatide, a recombinant parathyroid hormone fragment, not only increases bone mineral density but also increases bone connectivity.

CONCLUSIONS: Osteoporosis medications are usually safe, especially if used correctly with proper patient education. Treating osteopenia has not been found to be cost effective in women. However, obtaining a dual-energy X-ray absorptiometry scan and treating osteoporosis has resulted in cost savings in senior women living in community and nursing home residences. Pharmacists have multiple opportunities for preventing and treating osteoporosis.

KEYWORDS: Bisphosphonates, Calcitonin salmon, Bone remodeling, Postmenopausal osteoporosis, Raloxifene, Teriparatide

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Prevention of postmenopausal osteoporosis should begin during childhood because bone mass increases during the first 3 decades of life, reaching a peak at around the age of 30 years.¹ Men achieve a higher peak bone mass than women.² A slow loss of bone mass begins in both sexes when a person is in her or his mid-30s (Figure 1).³ A rapid loss of bone mass occurs after menopause in women because of estrogen deficiency.⁴ Women experience a loss of 10% to 25% of bone mass in the decade after menopause.² Age-related bone loss begins 10 to 15 years after menopause in women and at about the age of 55 years in men.² Age-related bone loss occurs at a similar rate in women and men.²

The goals of interventions to prevent and treat osteoporosis depend on a patient's life stage (i.e., age) and gender.² In both sexes, maximizing peak bone mass is sought during childhood and adolescence, and preserving bone mass by avoiding bone loss is the goal in adulthood in men and from young adulthood until menopause in women. During menopause and the early postmenopausal period, efforts are directed toward preventing the accelerated bone loss that typically occurs during this period. Prevention of further bone loss is the goal in men after the age of 55 years and from late postmenopausal period thereafter in women. In senior citizens of both sexes, prevention of falls and fractures is an additional key goal, especially in persons with a low bone mass.

Bone Physiology and Pathophysiology

Bone is a dynamic organ, with bone resorption by osteoclasts, bone formation by osteoblasts, bone mineralization, and quiescence occurring simultaneously.² Bone mineralization requires calcium, phosphate, and magnesium, which provide strength and rigidity.² Bone remodeling (i.e., resorption and formation) maintains skeletal strength by repairing microscopic damage.⁵ It also maintains the serum calcium concentration within the range needed for physiologic functions.⁵ Remodeling is regulated by estrogen, receptor activator of nuclear factor κ B (RANK) ligand, parathyroid hormone (PTH), calcitonin, vitamin D, prostaglandins, interleukins, growth factors, tissue necrosis factor, bone morphogenic proteins, and various other hormones and cytokines.⁵

The RANK ligand, a cytokine produced by osteoblasts, binds to a receptor on osteoclasts and promotes their differentiation, maturation, and activation.⁶ The RANK ligand also decreases apoptosis and increases the life span of osteoclasts. Activated osteoclasts attach to bone by integrins, forming a tight seal.² The osteoclast ruffled border secretes hydrogen ions, H⁺-ATPase, and the protease cathepsin K, which dissolve bone.^{2,4} Osteoblasts also produce osteoprotegerin to produce a negative feedback loop. Osteoprotegerin competes with the RANK ligand for binding at

FIGURE 1 Bone Health Therapeutic Algorithm

BMD=bone mineral density; CBC=complete blood count; DXA=dual-energy X-ray absorptiometry; OH=hydroxy; PTH=parathyroid hormone; TSH=thyroid-stimulating hormone.

receptors on osteoclasts, thereby preventing differentiation of osteoclasts and thus inhibition of bone resorption.⁴ Estrogen stimulates osteoblasts and inhibits osteoclasts.^{4,5}

Various conditions, diseases, medications, and aging can perturb normal bone remodeling. Menopause is associated with estrogen deficiency and thus opposing effects to premenopausal estrogen sufficiency. Diseases and medications can have multiple deleterious effects from decreasing gut calcium absorption to accelerating bone loss. Bone loss due to normal aging is a function of inadequate bone formation in addition to other aspects of aging, such as poor diet, comorbid conditions, and medications.

■ Osteoporosis Medication Pharmacology

Prescription drugs used to prevent or treat postmenopausal osteoporosis act on various parts of the bone remodeling process. They vary by U.S. Food and Drug Administration (FDA) approvals for prevention and/or treatment (Table 1). Since efficacy with osteoporosis medications was generally studied concomitantly with calcium or calcium and vitamin D, these supplements should

probably be used in combination with osteoporosis medications.

Bisphosphonates decrease osteoclast function by inhibiting osteoclast formation, recruitment, survival, and adherence to bone.² Etidronate, a first-generation bisphosphonate, is rarely used for the prevention or treatment of osteoporosis because the drug is associated with osteomalacia.² It is not approved by the FDA for osteoporosis indications. Alendronate, a more potent oral second-generation agent, was the first bisphosphonate approved by the FDA.⁷ Pamidronate, another second-generation injectable bisphosphonate, is not approved by the FDA for the prevention or treatment of osteoporosis. Oral risedronate, oral and injectable ibandronate, and injectable zoledronic acid (investigational for osteoporosis) are third-generation bisphosphonates with greater potency than second-generation agents.⁸ The binding affinities of bisphosphonates differ (in descending order from highest to lowest binding affinity, they are zoledronic acid, alendronate, ibandronate, risedronate, and etidronate), with possible implications for drug persistence in bone and longer duration of action.⁹

Prescription Drug Therapies for Prevention and Treatment of Postmenopausal Osteoporosis

TABLE 1 Medications Approved by the FDA for Prevention and Treatment of Osteoporosis

Drug	Indication	Dosage Forms and Recommended Dosing Frequency
Alendronate	Prevention of osteoporosis in postmenopausal women	35 mg tablet weekly 5 mg tablet daily
	Treatment of osteoporosis in postmenopausal women or to increase bone mass in men with osteoporosis	70 mg tablet weekly 70 mg tablet with 2,800 units vitamin D weekly 70 mg as oral solution weekly 10 mg tablet daily
	Treatment of glucocorticoid-induced osteoporosis* in men and women	5 mg tablet daily (10 mg tablet daily for postmenopausal women not receiving estrogen)
Risedronate	Prevention and treatment of osteoporosis in postmenopausal women	5 mg tablet daily 35 mg tablet weekly†
	Prevention and treatment of glucocorticoid-induced osteoporosis† in men and women	5 mg tablet daily
Ibandronate	Prevention of osteoporosis in postmenopausal women	2.5 mg tablet daily 150 mg tablet monthly‡
	Treatment of osteoporosis in postmenopausal women	2.5 mg tablet daily 150 mg tablet monthly‡ 3 mg as injection IV over 15-30 seconds every 3 months
Raloxifene	Prevention and treatment of postmenopausal osteoporosis	60 mg tablet daily
Calcitonin salmon	Treatment of osteoporosis in women 5 years postmenopausal	200 units daily alternating nares
Estrogen or estrogen and progestin therapy	Prevention of postmenopausal women	Various doses and products§
Teriparatide	Treatment of osteoporosis in women and men at high risk for fracture	20 mcg subcutaneous injection daily

* Glucocorticoid-induced osteoporosis is associated with long-term use of the equivalent of prednisone 7.5 mg/day or more.

† A 28-day blister pack is available with four 35-mg risedronate tablets to be taken weekly and twenty-four 1,250 mg calcium carbonate tablets (containing the equivalent of 500 mg elemental calcium) to be taken on days 2-7 of each 7-day treatment period.

‡ Missed doses of 150 mg ibandronate tablets may be taken only if more than 7 days will elapse before the next scheduled dose (two 150 mg tablets should not be taken within 1 week).

§ Minimal use after the Women's Health Initiative studies; however, small doses for short durations still advocated for menopausal symptom control or in patients who cannot tolerate any of the other osteoporosis medications.

FDA=U.S. Food and Drug Administration; IV=intravenous.

Selective estrogen receptor modulators (e.g., raloxifene) act as agonists at estrogen receptors on both osteoblasts and osteoclasts.² Calcitonin salmon acts directly on osteoclast receptors to suppress their activity.⁵ Denosumab mimics the action of osteoprotegerin by turning off osteoclast activity and is investigational.¹⁰ Postmenopausal estrogen therapy (ET) appears to directly inhibit osteoclasts and is approved for prevention although with limited use after the Women's Health Initiative trials.⁵

Although bone resorption is associated with hyperparathyroidism and large doses of parathyroid hormone, smaller doses increase osteoblast differentiation and activity. These latter effects are achieved with teriparatide, a recombinant human parathyroid hormone fragment,¹¹ and investigational PTH 1-84.¹²

Several investigational agents are being explored to inhibit other aspects of resorption and to enhance other aspects of

formation. Investigational osteoporosis drug classes include integrin receptor antagonists, cathepsin K inhibitors, recombinant human insulin-like growth factor 1, H⁺ATPase inhibitors, interleukin-1 receptors, calciometrics, and calciolytics.⁶ Efforts to develop compounds with the characteristics of osteoprotegerin that bind to the RANK receptor and inhibit osteoclast activation have not been successful because of antibody formation.

■ Treatment Algorithm

Bone mineral density (BMD) testing (see the preceding article by Kamel in this supplement) of the spine and hip is appropriate before initiating treatment with prescription osteoporosis medications in women aged 65 years and older, women aged 60 to 64 years who are at increased risk for osteoporotic fractures, and men at increased risk for fractures (Figure 1).² Treatment with

osteoporosis medications may be considered without first testing for BMD in men and women with a fragility fracture or using systemic glucocorticoids on a long-term basis.² A Z-score less than -2.0 (see the preceding article by Kamel in this supplement) suggests the need for a diagnostic work-up to identify a secondary cause of osteoporosis. Drug therapy is not indicated for patients with a normal BMD (a T-score >-1), and its use is controversial in patients with osteopenia (a T-score between -1 and -2.5) and most likely is not cost effective.¹³ BMD testing should be performed every 1 to 5 years in patients with normal BMD or osteopenia.² If a patient has spinal osteoporosis (i.e., a spine T-score <-2.5), a bisphosphonate, raloxifene, or calcitonin salmon could be tried, in that order. All of these therapies have been shown to decrease vertebral fractures, but only the bisphosphonates have been shown to decrease the incidence of hip fractures.² Therefore, if hip osteoporosis is present (i.e., a hip T-score <-2.5), treatment with a bisphosphonate is preferred. If the patient is intolerant to oral bisphosphonates, a parenteral bisphosphonate, teriparatide, raloxifene, and calcitonin salmon are alternatives.²

■ Bisphosphonates

Bisphosphonates are the drugs of choice for preventing and treating osteoporosis.² The drugs increase BMD in a dose-dependent manner, and they produce significant reductions in the risk of hip, spine, and nonvertebral fractures.^{2,14-17} The efficacy of bisphosphonates has been demonstrated in both women and men, including the elderly.² The response to bisphosphonates is greater in patients with a low BMD than in patients with a high BMD.¹⁷ The increase in BMD from bisphosphonates is enhanced by concomitant ET or raloxifene² but is inhibited by concomitant PTH/teriparatide therapy. Adequate calcium and vitamin D intake is also needed for the beneficial effects of bisphosphonates to be observed.

Bisphosphonates can irritate the upper gastrointestinal (GI) mucosa, but the drugs are relatively safe if the patient has no serious underlying GI disorders. Bisphosphonates should not be used in patients with esophageal strictures or achalasia or for those who are unable to stand or sit upright for at least 30 minutes (at least 60 minutes for ibandronate) after drug administration.^{7,18-20} Bisphosphonates may be used in patients with gastroesophageal reflux disease and patients who take aspirin or nonsteroidal anti-inflammatory drugs. Nausea, abdominal pain, and dyspepsia are the most common adverse effects from bisphosphonates.² Esophageal perforation and bleeding are rare. Switching to a formulation that is administered weekly or monthly instead of daily might minimize these effects. The cells that line the GI tract regenerate in about 5 days, with the longer dosing intervals allowing for cellular regeneration between doses.²

Osteonecrosis of the jaw has been infrequently reported in patients receiving bisphosphonates (particularly with the injectable agents pamidronate and zoledronic acid), primarily in patients receiving chemotherapy or corticosteroids or in associa-

tion with tooth extraction, surgery, or infection.^{7,18-22} Muscle, bone, and joint pain that usually abates after discontinuing the drug and a flu-like syndrome, with fever, chills, flushing, and musculoskeletal pain, also have been reported.^{7,18-20,22} Bisphosphonates should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of a lack of data.^{7,18-20}

Alendronate

Long-term efficacy and safety data are available from more than 10 years of alendronate use. Progressive increases in spine and hip BMD were observed over a 10-year period in a randomized, double-blind study of 247 postmenopausal women with osteoporosis who received the bisphosphonate alendronate 5 mg/day or 10 mg/day.²³ The greatest increases in BMD were observed during the first 3 to 5 years of treatment and with the 10-mg dose. A tendency to reach a plateau in hip BMD was observed after about 5 years, but progressive increases in spine BMD continued throughout the 10-year period. The 10-year increases in BMD from baseline after 10 mg per day for 10 years was 13.7% for lumbar spine, 10.3% for trochanter, 5.4% for femoral neck, and 6.7% for proximal femur.

The increased BMD from bisphosphonate therapy is maintained or slightly diminished after discontinuation of the drug but is better than placebo therapy. The effects on spine and hip BMD from alendronate 2.5 to 20 mg daily for 2, 4, or 6 years followed by no treatment for 7, 5, or 3 years, respectively, were evaluated in a placebo-controlled study of 203 postmenopausal women.²⁴ The rate of bone loss after all doses of alendronate discontinuation was comparable to the rate observed with placebo, thus due to normal aging, not related to a drug-induced accelerated rate of bone loss such that is seen with ET discontinuation. A benefit from alendronate over placebo was observed for up to 7 years after discontinuation of the drug. This study provides valuable information about duration of therapy, but no there is no consensus yet on how long to continue bisphosphonate therapy or at what point to reinstitute therapy.

Risedronate

Clinical trials have also documented long-term (up to 5 years) BMD efficacy and safety with risedronate. In a 1-year randomized, double-blind study of 1,053 women with postmenopausal osteoporosis (Fosamax Actonel Comparison Trial [FACT]), the efficacy of once-weekly risedronate (35 mg) and once-weekly alendronate (70 mg) in increasing BMD was compared.²⁵ Significantly greater increases in BMD were observed with alendronate than with risedronate. The differences measured in the BMD were 1.4% for hip trochanter ($P < 0.001$), 1.0% for total hip ($P < 0.001$), 0.7% for femoral neck ($P < 0.01$), and 1.2% for lumbar spine ($P < 0.001$). However, the clinical significance of these findings cannot be extrapolated to a difference in the impact of the drugs on fractures. This study most likely will never be

conducted because of the large number of patients required. With the evolving science of bone remodeling and osteoporosis, a medication's impact on bone structure will most likely become more important than BMD changes only.

In a 2-week study of 515 healthy, postmenopausal women, risedronate 5 mg/day was associated with a significantly lower risk of gastric ulcers than alendronate 10 mg/day, 4.1% versus 13.2%, respectively ($P < 0.001$), potentially because of differences in the GI damage from pyridinyl bisphosphonates (e.g., risedronate) and amino bisphosphonates (e.g., alendronate).²⁶ Comparative studies over a longer duration and with weekly therapy are needed to determine whether the risk of upper GI adverse effects from these bisphosphonates differs clinically.

Ibandronate

Ibandronate is the newest bisphosphonate to reach the market. It is unique among bisphosphonates because it may be given orally on a monthly or daily basis or as a quarterly injection. Potential advantages of an injectable bisphosphonate formulation include a lower risk of GI adverse effects because of less irritation of the GI mucosa and improved bioavailability and patient adherence. Although the use of the injectable route of administration is not as convenient and is more costly than the oral route, it might be preferred in patients in a long-term-care setting who cannot remain sitting or standing for at least 30 to 60 minutes after drug administration or in patients with GI diseases in whom oral therapy is contraindicated.

The efficacy of oral ibandronate 2.5 mg/day with calcium 500 mg and vitamin D 400 units in reducing the risk of fractures was demonstrated in a pivotal, 3-year, randomized, double-blind, placebo-controlled, parallel-group study of 2,946 postmenopausal women with osteoporosis.¹⁷ Ibandronate produced significantly greater increases from baseline in lumbar spine (6.5% vs. 1.3%, respectively; $P < 0.0001$) and hip BMD (3.4% vs. -0.7%, respectively; $P < 0.0001$) than placebo. The rate of new vertebral fractures was 4.7% with ibandronate and 9.6% with placebo, representing a 62% reduction ($P = 0.0001$) in fractures with the bisphosphonate treatment. Ibandronate produced a significant 49% reduction ($P = 0.0117$) in clinical vertebral fractures (i.e., fractures confirmed by X-ray and accompanied by pain), representing an absolute difference of 2.5%. The incidence of nonvertebral fractures was similar with ibandronate (9.1%) and placebo (8.2%). However, in a post hoc analysis of a subset of high-risk patients with a particularly low femoral neck BMD (T-score < -3.0), ibandronate therapy was associated with a significantly lower incidence of nonvertebral fractures than placebo (about 7.5% vs. 14.8%, respectively; 69% relative risk reduction, $P = 0.013$). The incidence of adverse drug reactions was similar with ibandronate (20%) and placebo (18%).

The efficacy of using a monthly dose of ibandronate instead of a daily dose for treating postmenopausal osteoporosis was demonstrated in a 2-year, randomized, double-blind, phase 3,

noninferiority trial known as the Monthly Oral Ibandronate in Ladies (MOBILE) study.²⁷ Several monthly doses (100 mg as 2 divided doses on 2 consecutive days, 100 mg on a single day and 150 mg on a single day) were compared with 2.5 mg/day in 1,609 women with postmenopausal osteoporosis. The women also took supplements (calcium 500 mg and vitamin D 400 units) daily. After 1 year of treatment, all of the monthly ibandronate doses were judged noninferior to the daily dose for increasing lumbar spine, hip, femoral neck, and trochanter BMD, with the greatest increases from baseline in the monthly 150-mg dose group. The incidence of adverse effects leading to withdrawal from the study was similar with monthly drug administration (5.1%-6.3%) and daily therapy (7.3%).

Ibandronate 3 mg intravenous (IV) every 3 months and 2.5 mg/day orally were compared in a double-blind, double-dummy, phase 3 study of 1,395 women with postmenopausal osteoporosis (Dosing IntraVenous Administration [DIVA] study).²⁸ Calcium (500 mg/day) and vitamin D (400 units/day) supplements were provided to all women. After 1 year of treatment, significantly greater increases from baseline in lumbar spine BMD were associated with IV therapy (4.8%) than with oral therapy (3.8%; $P < 0.001$). Increases in total hip, femoral neck, and trochanter BMD also were greater with IV therapy than oral therapy.

Patient preferences for weekly alendronate 70-mg doses or monthly ibandronate 150-mg doses were evaluated in a 6-month, prospective, randomized, open-label study of 342 women with postmenopausal osteoporosis (Boniva Alendronate Trial in Osteoporosis [BALTO] study).²⁹ A 2-period, 2-sequence crossover treatment design was used. Significantly more women (66%) preferred monthly ibandronate therapy than weekly alendronate therapy (27%; $P < 0.0001$). Seven percent of participants had no preference for either drug or dosing frequency. Greater tolerability of adverse effects was a reason for 17% of patients who preferred monthly ibandronate and 4% of patients who preferred weekly alendronate. The incidence of adverse effects was similar, with approximately 12% of both groups reporting GI adverse effects.

Zoledronic Acid

Zoledronic acid (zoledronate), a potent, third-generation injectable bisphosphonate, is currently approved by the FDA for bone metastasis and malignant hypercalcemia and investigational for the prevention or treatment of osteoporosis. The effects of 5 different IV zoledronic acid regimens on BMD were evaluated in a 1-year, randomized, double-blind, placebo-controlled study of 351 postmenopausal women with low BMD.³⁰ Zoledronic acid 0.25 mg, 0.5 mg, or 1 mg or placebo were given at 3-month intervals. A fifth group received a single 4-mg dose, and the sixth group received two 2-mg doses 6 months apart. All 5 zoledronic acid regimens produced significantly greater but somewhat similar BMD increases from baseline compared with the mean placebo group response in lumbar spine (4.3 to 5.1% greater response, $P < 0.001$) and femoral neck BMD (3.1 to 2.5% greater response,

$P < 0.001$). All zoledronic acid regimens suppressed biochemical markers of bone resorption to a significantly greater extent than placebo throughout the study. The incidence of myalgia and pyrexia was higher in the zoledronic acid groups than in the placebo group. Treatment related side effects were 45% to 67% in the zoledronic acid groups versus 27% in the placebo group ($P < 0.05$); however, the treatment-related dropout rates for zoledronic acid (3% to 7%) were similar to the placebo group (2%).

■ Patient Education

Patient education is vital for the safe and effective use of bisphosphonates to prevent and treat osteoporosis. The bioavailability of oral bisphosphonates is low, and food and beverages other than plain water can further reduce bioavailability. Therefore, patients should be advised to take the medication at least 30 minutes before the first food or beverage (other than plain water) of the day, and take the medication only with a full (6-8 oz.) glass of plain water (not mineral water, orange juice, coffee, sodas, or milk).^{7,18-20} Patients also should be advised not to lie down for at least 30 minutes (60 minutes for ibandronate) after taking the medication to facilitate delivery to the stomach and reduce the risk for esophageal irritation.^{7,18-20} Calcium and other multivalent cations, including antacids, calcium supplements, and multivitamins, should be taken at least 60 minutes after the bisphosphonate because the cations may interfere with bisphosphonate absorption.^{7,18-20} Patients also should be warned to report difficult or painful swallowing or heartburn to their health care provider. Patient counseling should be ongoing and adherence to therapy should be assessed often. To improve adherence with the once-monthly ibandronate regimen, patients have the option of receiving reminders by regular or electronic mail from the manufacturer (www.myboniva.com).

Although a 30-minute fast is recommended, longer fasts could increase bisphosphonate absorption, according to an alendronate pharmacokinetic study³¹ and a recent ibandronate study.³² The impact on efficacy of changing the duration of fasting after administration of oral ibandronate 2.5 mg/day from 60 minutes to 30 minutes was evaluated in a 48-week, multicenter, open-label, randomized, parallel-group, noninferiority study of 184 women with postmenopausal osteoporosis.³² The relative increase from baseline in lumbar spine BMD was lower in the 30-minute fast group (3%) than that in the 60-minute fast group (5%). The increase in total hip BMD also was lower with the 30-minute fast than with the 60-minute fast (2% vs. 3%, respectively). Thus, a 30-minute fast did not meet the criteria for noninferiority to a 60-minute fast, so a 60-minute fast is recommended after oral administration of ibandronate.²⁰

Ibandronate injection should be administered by health care professionals who have been educated regarding the unique requirements for handling and administering the medication. Ibandronate injection is provided in a kit with a single-use, prefilled, glass syringe containing 3 mg/3 mL of the drug, with

a 23-gauge, 1-inch needle and an alcohol wipe. The kits should be stored at controlled room temperature (59°F-86°F). Reconstitution and refrigeration of the drug are not required. The drug should not be mixed with calcium-containing solutions or other IV medications. Ibandronate injection is administered by rapid IV injection over 15 to 30 seconds, using caution not to give it intra-arterially. Treatment with IV bisphosphonates has been associated with renal toxicity, with a risk that appears to be inversely related to the rate of drug administration. The rapid injection of ibandronate over 15 to 30 seconds was not associated with acute renal failure in controlled clinical trials.³³

■ Raloxifene

Raloxifene is currently the only selective estrogen receptor modulator (SERM) approved by the FDA for the prevention and treatment of osteoporosis in postmenopausal women. Positive clinical osteoporosis trial data exist for another SERM, tamoxifen; however, it is only approved by the FDA for the prevention of breast cancer. Other SERMs are in development.

Raloxifene acts as an estrogen agonist in bone and on lipids and as an estrogen antagonist in breast and uterine tissues.³⁴ Raloxifene increases spine and hip BMD, but not to the same extent as bisphosphonates or ET.^{2,3} Raloxifene reduces the risk of vertebral fractures by 30% to 50% in women with postmenopausal osteoporosis, but it does not affect the rate of nonvertebral fractures.^{5,35-38} Adding raloxifene to alendronate does not produce greater increases in BMD than using alendronate alone; however, combination therapy is better than raloxifene alone.³⁷ Whether changes in BMD predict an impact on fractures from raloxifene therapy is not clear since fracture prevention does not correlate with BMD changes for this medication.

To determine if raloxifene had a cardiovascular effect and could add additional benefit during osteoporosis therapy, its effects on lipids and cardiovascular disease and mortality have been evaluated. Decreases in total and low-density lipoprotein cholesterol concentrations with little change in high-density lipoprotein cholesterol and triglyceride concentrations are associated with raloxifene therapy, which are lower than those achieved with ET/hormone therapy (HT).³⁸ Unlike ET, raloxifene is not associated with negative cardiovascular events. A secondary analysis of cardiovascular event data (i.e., coronary and cerebrovascular events, including myocardial infarction, unstable angina, coronary ischemia, stroke, and transient ischemic attack) from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial revealed that raloxifene treatment over a 4-year period did not significantly affect the risk of cardiovascular events.³⁹ However, in a subset of women who were at increased risk for cardiovascular events because of the presence of multiple cardiovascular risk factors, a history of coronary events, or a prior revascularization procedure, raloxifene significantly reduced the risk of cardiovascular events compared with placebo. Preliminary data from the Raloxifene Use for The Heart trial (RUTH) found no increases or

decreases in heart disease or mortality with raloxifene (newsroom.lilly.com/ReleaseDetail.cfm? ReleaseID=192692).

Raloxifene's role in osteoporosis therapy could change, at least for a subset of women with or at risk for breast cancer, if it were to receive an FDA approval for breast cancer prevention. The effect of raloxifene on the risk for breast cancer was evaluated in the MORE study.⁴⁰ In this randomized, double-blind trial, 7,705 women with postmenopausal osteoporosis received raloxifene 120 mg/day or 60 mg/day or placebo and were followed for a median of 40 months. Raloxifene significantly reduced the incidence of invasive breast cancer by 76%, with 126 the number of women needed to treat to prevent 1 case of breast cancer (relative risk reduction changed from 4.3 on placebo to 1.5 with raloxifene). Raloxifene did not increase the risk of endometrial cancer; it increased the risk of venous thromboembolic disease 3-fold, but the incidence was still low (18 cases in 2,557 women).

Raloxifene 60 mg is taken orally once daily. The drug causes hot flushes in as many as 1 in 4 women.³⁸ Raloxifene is associated with an increased risk of thromboembolism (e.g., deep vein thrombosis), although the incidence is low and it is contraindicated in women with a history of venous thrombosis.³⁸

Hormone Therapy

HT (estrogen plus a progestin or, for women without a uterus, estrogen alone [ET]) increases BMD in women with or at risk for postmenopausal osteoporosis.⁴¹ A reduced risk for vertebral and hip fractures has been reported in postmenopausal women receiving estrogen plus a progestin, and a reduced risk of hip fractures has been observed in postmenopausal women who received estrogen alone.⁴²⁻⁴⁴ However, the use of HT to prevent and treat osteoporosis has fallen out of favor because of the findings from the Women's Health Initiative and other research suggesting an increased risk of stroke and cardiovascular disease early in the course of therapy in patients receiving HT or ET.^{43,44} The risks outweigh the benefits of ET or HT in most women, although ET or HT is still approved by the FDA for the prevention (not treatment) of postmenopausal osteoporosis in women who are at significant risk and for whom nonestrogen medications are not appropriate.⁴⁵ HT is still advocated for short-term use to manage vasomotor and urogenital symptoms associated with menopause. The lowest effective dose should be used.

Calcitonin Salmon

Calcitonin is a natural polypeptide hormone secreted by the thyroid gland in response to high serum calcium concentrations. It decreases bone resorption. Calcitonin salmon is a synthetic form with the same amino acid sequence as that of calcitonin of salmon origin. Calcitonin salmon is approved for the treatment (but not prevention) of postmenopausal osteoporosis in women who are more than 5 years beyond menopause and have a low bone mass.^{46,47} The drug is available as an injection for subcutaneous (SC) or intramuscular administration and a nasal spray. The

injectable form is seldom used because it can cause nausea and facial flushing and the nasal spray is better tolerated.⁵

Calcitonin salmon nasal spray 200 units/day decreased the risk of new vertebral fractures by about one third (18% vs. 26%, respectively; $P=0.03$) in a large, 5-year study of postmenopausal women with osteoporosis.⁴⁸ Of note, the withdrawal rate in this study was 59%. However, the drug does not appear to decrease the risk of hip fractures. There is evidence of a plateau in the effect of calcitonin salmon on markers of bone resorption after 8 weeks of treatment, suggesting that intermittent administration may be appropriate.⁴⁹ Further study is needed.

An analgesic effect from intranasal calcitonin salmon has been reported in patients with osteoporotic vertebral fractures.^{50,51} The time to onset of analgesia is as little as 1 week.⁵¹ Analgesia might be the result of endorphin release, an anti-inflammatory effect due to decreased prostaglandin synthesis, direct calcitonin receptor stimulation, or decreased osteoclastic activity.^{51,52} The analgesic effect from calcitonin salmon may reduce the requirements for analgesic medications.⁵¹

Rhinitis and epistaxis are the most common adverse effects from calcitonin salmon nasal spray.⁴⁶ The spray is given as a single daily 200-unit dose. Patients should be instructed to alternate nares daily.

Unopened bottles of calcitonin salmon nasal spray should be stored in the refrigerator, but the bottle in use may be stored at room temperature for up to 35 days.⁴⁶ Patients should be instructed how to prime the pump before the first dose, but priming is not required for subsequent doses.

Teriparatide

Teriparatide (recombinant human PTH) contains the first 34 amino acids of the 84 amino acids in human PTH. It is administered as a single daily dose by SC injection into the thigh or abdominal wall.⁵³ A recombinant human PTH product with all 84 amino acids might be approved by the FDA for the treatment of postmenopausal osteoporosis in the near future. Administration of this product by the SC route also appears to increase BMD and reduce the risk of vertebral fractures.¹¹

At therapeutic doses, teriparatide increases bone formation by stimulating osteoblast replication and inhibiting osteoblast apoptosis.⁵ Teriparatide increases the thickness of outer cortical bone and increases the connectivity of trabecular bone (the interior porous bone found in vertebrae and other bones).⁵⁴ These changes increase bone strength and make teriparatide unique among osteoporosis therapies. Although bisphosphonates increase BMD, they do not affect connectivity or strength. Increases in lumbar spine BMD of 9.7% ($P<0.001$) and femoral neck of 2.8% ($P<0.001$) were significantly greater than placebo.⁵⁵ Teriparatide significantly reduced the risk of new vertebral (5% vs. 14%, respectively; relative risk 0.35; 95% confidence interval [CI], 0.22-0.55) and nonvertebral fragility fractures (3% vs. 6%, respectively; relative risk 0.47; 95% CI, 0.25-0.88) compared with placebo in postmenopausal women with osteoporosis.

Teriparatide may be used in conjunction with raloxifene or HT. However, teriparatide should not be used in combination with bisphosphonates because they may reduce the effects of teriparatide.^{56,57} Bisphosphonates can be used before or after PTH therapy, with potentially better results in bisphosphonate-naïve patients receiving the bisphosphonate after PTH therapy.

Teriparatide can cause orthostatic hypotension, so patients should be advised to position themselves so that they can sit or lie down if they feel lightheaded after drug administration. Such reactions usually resolve within a few minutes to a few hours and do not preclude continued use of the drug.⁵³ Large doses of teriparatide were associated with an increased incidence of osteosarcoma in animal studies, but the relevance of these findings for humans are questionable. Osteosarcoma has not been observed in humans in phase 4 postmarketing surveillance. Teriparatide should not be used for more than 2 years because the safety and efficacy of the drug for periods longer than 2 years have not been evaluated.⁵³

Patient counseling should address the proper storage and administration of teriparatide. The drug is a clear, colorless, 250-mcg/mL solution provided in prefilled pens containing twenty-eight 20-mcg doses. Teriparatide may be self-administered by the patient or a caregiver once she or he receives instructions on proper priming and use of the pen. The drug should be stored under refrigeration (36°F -46°F) and administered without allowing it to warm to room temperature.⁵³ The pen should be recapped between uses. Missed doses should be administered as soon as they are remembered, but no more than 1 injection should be administered on the same day.⁵³

Denosumab

Denosumab (formerly known as AMG 162) is a humanized monoclonal antibody specific for the RANK ligand. It inhibits osteoclast activation and activity.⁵⁸ The efficacy and safety of denosumab were evaluated in a 12-month, phase 2, randomized, controlled trial of 412 postmenopausal women with low BMD.⁵⁹ Subjects were randomly assigned to receive denosumab 6 mg, 14 mg, or 30 mg SC every 3 months; denosumab 14 mg, 60 mg, 100 mg, or 210 mg SC every 6 months; open-label alendronate 70 mg orally once weekly; or placebo. All patients received calcium and vitamin D supplementation. Denosumab produced increases in lumbar spine (3.0%-6.7%), total hip (1.9%-3.6%), and distal radius (0.4%-1.3%) BMD that exceeded those produced by placebo ($P < 0.001$) and were comparable to or greater than those produced by alendronate (4.6%, 2.1%, -0.5%, respectively). However, small increases in risk for neoplasm (1.9%) and infection (1.0%) were associated with denosumab treatment compared with alendronate (0% for both) or placebo (0% for both). Additional denosumab safety data are needed. Phase 3 clinical trials of denosumab in postmenopausal women with osteoporosis began in 2004.

TABLE 2 Incremental Cost-Effectiveness Ratio (\$) for Using Alendronate in Postmenopausal Women^{13,61 *}

Age (Years)	Femoral Neck T Score			
	-1.5	-2.0	-2.4	<-2.5
55	256,000	94,000	74,000	NE
65	284,000	92,000	71,000	40,100
75	332,000	109,000	86,000	5,600
85	NE	NE	NE	Cost savings
95	NE	NE	NE	Cost savings

* Dollar figures represent the cost per quality-adjusted life-year gained by using alendronate instead of no treatment. Values below \$50,000 per year are usually considered acceptable in the United States.

NE=not evaluated.

Economics

Prescription osteoporosis drug therapies (e.g., bisphosphonates, raloxifene, calcitonin salmon, teriparatide) are more costly than nonprescription calcium and vitamin D supplements, most of which cost \$5 to \$15 per month. The monthly cost of prescription osteoporosis drugs ranges from a low of about \$85 for oral bisphosphonates to a high of around \$700 for teriparatide. The monthly costs of raloxifene and calcitonin salmon are slightly higher than the oral bisphosphonates. The cost of ibandronate injection is higher than that of oral bisphosphonates, including oral ibandronate, but the greater tolerability might justify the added expense. The high cost of teriparatide might be justified because it is the only osteoporosis drug that increases bone formation and connectivity. Depending on the Medicare Part D plan, usually alendronate or risendronate are covered with varying copays per plan for preferred medications since generic agents are not available. Ibandronate is either at equal bisphosphonate coverage or at the nonpreferred or higher tier copay. Raloxifene and calcitonin salmon are covered at the preferred or middle tier copay. Teriparatide is usually listed as nonpreferred or in the highest tier copay, and prior authorization is often required.

A Markov cost-utility analysis of the benefit of alendronate (compared with no treatment) in postmenopausal women with osteopenia (i.e., at risk for osteoporosis, T-score -1.5 to -2.4) was performed from a societal perspective.¹³ Five years of alendronate therapy was assumed because of the plateau in effect on hip BMD after this duration of treatment.²³ The analysis used fracture data from the Fracture Intervention Trial, a randomized, blinded, placebo-controlled trial of alendronate.⁶⁰ Medicare costs from 2001 and health care utilization data from an Olmsted County, Minnesota, database also were used.

The incremental cost-effectiveness ratio (i.e., cost per quality-adjusted life-year [QALY] gained) for alendronate therapy in postmenopausal women with osteopenia was determined for 3 different

ages and 3 different femoral neck T-scores (Table 2). The investigators concluded that alendronate therapy is not cost effective in any of these scenarios, assuming a societal willingness to pay \$50,000 per QALY. However, the results of the cost-utility analysis changed when the influence of additional risk factors for fracture other than low BMD (e.g., a family history of fractures) was assessed for 65-year-old postmenopausal women with osteopenia and a T-score of -2.0. As the relative risk for fracture (adjusted for BMD) from added risk factors increased, the cost per QALY decreased. Alendronate treatment became cost effective (i.e., the cost per QALY fell below \$50,000) for these patients when the relative risk for fractures reached 2.0 or higher (i.e., a 2-fold or greater increase in the relative risk for fracture). The World Health Organization currently is analyzing risk factors for fracture that will facilitate cost-effectiveness analyses and patient selection for therapy in the future.

A similar cost-utility model was developed by the same investigators to evaluate the cost-effectiveness from a societal perspective of universal bone densitometry screening measurements in women aged 65 years or older followed by 5 years of alendronate treatment in those with a femoral neck T-score of -2.5 or lower (i.e., a diagnosis of osteoporosis).⁶¹ The cost per QALY gained by using alendronate instead of no treatment was \$43,000 for women aged 65 years and \$5,600 for women aged 75 years. In women aged 85 years living in nursing homes, the cost per QALY gained from alendronate therapy was \$7,300 to \$12,900. Alendronate was cost saving for women aged 85 and 95 years living in the community (i.e., ambulatory) and women aged 95 years living in nursing homes. Thus, universal bone densitometry screening for women aged 65 years or older and the use of alendronate therapy for women with osteoporosis were cost effective.

Conclusion

Preventing the accelerated bone loss associated with the early postmenopausal period and decreasing aging-related decreases in bone density are the primary goals of prescription osteoporosis drug therapy. Bisphosphonates are the drugs of choice for preventing and treating postmenopausal osteoporosis. Increasing the dosing interval might increase patient acceptance and adherence by improving convenience. Alternatives for patients who cannot take bisphosphonates include raloxifene and calcitonin salmon. Teriparatide is used to build new bone in patients with significant osteoporosis and should not be used concomitantly with a bisphosphonate. The cost-effectiveness of osteoporosis drug therapies depends on patient age, BMD, and other risk factors for the disease; however, treating osteoporosis with a bisphosphonate in senior women is cost effective and using it to prevent preventing osteoporosis in women with osteopenia is not.

DISCLOSURES

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REFERENCES

- Hodgson SF, Watts NB, Bilezikian JP, et al. for the AACE Osteoporosis Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. *Endocr Pract.* 2003;9:544-64.
- O'Connell MB, Seaton TL. Osteoporosis and osteomalacia. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York, NY: McGraw-Hill; 2005: 1645-69.
- U.S. Department of Health and Human Services. The 2004 Surgeon General's report on bone health and osteoporosis: what it means to you. Available at: <http://hhs.gov/surgeongeneral/library/bonehealth/docs/OsteoBrochure1mar05.pdf>. Accessed April 20, 2006.
- U.S. Department of Health and Human Services. Chapter 2: The basics of bone in health and disease. In: *Bone Health and Osteoporosis: A Report of the Surgeon General (2004)*. Available at: http://www.surgeongeneral.gov/library/bonehealth/chapter_2.html. Accessed April 26, 2006.
- Lindsay R, Cosman F. Osteoporosis. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York, NY: McGraw-Hill; 2005:2268-78.
- Vondracek SF, Chen JT, Csako G. Osteoporosis—pathophysiology and new drug development. *Clin Rev Bone Mineral Metab.* 2004;2:293-313.
- Fosamax [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; February 2006.
- Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacother.* 2005;39:668-77.
- Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone: Differences in interactions with hydroxyapatite. *Bone.* 2006;38:617-27.
- McClung MR, Lewiecki EM, Cohen SB et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med.* 2006; 354:821-31.
- Shrader SP, Ragucci KR. Parathyroid hormone (1-84) and treatment of osteoporosis. *Ann Pharmacother.* 2005;39:1511-16.
- Adis International Ltd. ALX 111: ALX-11, parathyroid hormone (1-84)-NPS Allelix, PREOS, PTH, recombinant human parathyroid hormone, rhPTH (1-84). *Drugs RD.* 2003; 4:231-35.
- Schousboe JT, Nyman JA, Kane RL, Ensrud KE. Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women. *Ann Intern Med.* 2005;142:734-41.
- North American Menopause Society. Management of postmenopausal osteoporosis: position statement of the North American Menopause Society. *Menopause.* 2002;9:84-101.
- Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev.* 2002;23:508-16.
- Cranney A, Tugwell P, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev.* 2002;23:517-23.
- Chestnut III CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res.* 2004;19:1241-49.
- Actonel [package insert]. Cincinnati, OH: Procter & Gamble Pharmaceuticals, Inc; January 2006.

19. Woo SB, Hellstein JW, Kalmar JR. Systemic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med.* 2006;144:753-61.
20. Boniva tablets [package insert]. Nutley, NJ: Roche Laboratories, Inc; March 2005.
21. Aredia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2005.
22. Zometa [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2005.
23. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med.* 2004;350:1189-99.
24. Bagger YZ, Tanko LB, Alexandersen P, Ravn P, Christiansen C. Alendronate has a residual effect on bone mass in postmenopausal Danish women up to 7 years after treatment withdrawal. *Bone.* 2003;33:301-07.
25. Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res.* 2005;20:141-51.
26. Lanza FL, Hunt RH, Thomson AB, Provenza JM, Blank MA. Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women. *Gastroenterology.* 2000;119:631-38.
27. Miller PD, McClung MR, Macovei L, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res.* 2005;20:1315-22.
28. Bolognese M, Reid DM, Langdahl B, et al. Efficacy of intravenous ibandronate injections in postmenopausal osteoporosis: 1-year findings from DIVA [abstract]. *J Bone Miner Res.* 05;20(suppl 1):S96.
29. Emkey R, Koltun W, Beusterien K, et al. Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Boniva Alendronate Trial in Osteoporosis (BALTO). *Curr Med Res Opin.* 2005;21:1895-1903.
30. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med.* 2002;346:653-61.
31. Gertz BJ, Holland SD, Kline WF, et al. Studies of the oral bioavailability of alendronate. *Clin Pharmacol Ther.* 1995;58:288-98.
32. Tanko LB, McClung MR, Schimmer RC, Mahoney P, Christiansen C. The efficacy of 48-week oral ibandronate treatment in postmenopausal osteoporosis when taken 30 versus 60 minutes before breakfast. *Bone.* 2003;32:421-26.
33. Boniva injection [package insert]. Nutley, NJ: Roche Laboratories, Inc; January 2006.
34. Delaney MF. Strategies for the prevention and treatment of osteoporosis during early postmenopause. *Am J Obstet Gynecol.* 2006;194(suppl 2):S12-S23.
35. Delmas PD, Ensrud KE, Adachi JD, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab.* 2002;87:3609-17.
36. Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. *Endocr Rev.* 2002;23:524-28.
37. Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab.* 2002;87:985-92.
38. McEvoy GK, ed. Raloxifene hydrochloride. In: *AHFS Drug Information* 2006. Bethesda, MD: American Society of Health-System Pharmacists; 2006:3059-65.
39. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA.* 2002;287:847-57.
40. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA.* 1999;281:2189-97.
41. Wells G, Tugwell P, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocr Rev.* 2002;23:529-39.
42. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* 2003;290:1729-38.
43. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-33.
44. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291:1701-12.
45. Prempro and Premphase [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc; July 2005.
46. Miacalcin nasal spray [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2003.
47. Miacalcin injection, synthetic [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2002.
48. Chestnut CH 3rd, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med.* 2000;109:267-76.
49. Kraenzlin ME, Seibel MJ, Trechsel U, et al. The effect of intranasal salmon calcitonin on postmenopausal bone turnover as assessed by biochemical markers: evidence of maximal effect after 8 weeks of continuous treatment. *Calcif Tissue Int.* 1996;58:216-20.
50. Pun KK, Chan LW. Analgesic effect of intranasal salmon calcitonin in the treatment of osteoporotic vertebral fractures. *Clin Ther.* 1989;11:205-09.
51. Silverman SL, Azria M. The analgesic role of calcitonin following osteoporotic fracture. *Osteoporos Int.* 2002;13:858-67.
52. Lyrithis GP, Trovas G. Analgesic effects of calcitonin. *Bone.* 2002;30(suppl 5):71S-74S.
53. Forteo [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2004.
54. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1-34) [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res.* 2003;18:1932-41.
55. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344:1434-41.
56. Black DM, Greenspan SL, Ensrud KE, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med.* 2003;349:1207-15.
57. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med.* 2003;349:1216-26.
58. McClung MR. Inhibition of RANKL as a treatment for osteoporosis: preclinical and early clinical studies. *Curr Osteoporos Rep.* 2006;4:28-33.
59. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med.* 2006;354: 821-31.
60. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA.* 1998;280:2077-82.
61. Schousboe JT, Ensrud KE, Nyman JA, Melton LG 3rd, Kane RL. Universal bone densitometry screening combined with alendronate therapy for those diagnosed with osteoporosis is highly cost-effective for elderly women. *J Am Geriatr Soc.* 2005;53:1697-704.