Alendronate sodium, an aminobisphosphonate, has been approved by the Food and Drug Administration for the prevention and treatment of osteoporosis in postmenopausal women, thus providing an effective alternative to estrogen replacement therapy in women who cannot or will not take estrogen. Large, randomized, controlled trials have demonstrated approximately a 50% reduction in vertebral, hip, and wrist fractures. Efficacy and safety beyond 3 years has not been determined. To avoid esophagitis and maximize absorption, alendronate should be taken with 180 to 240 mL of water on arising for the day, allowing at least 30 minutes before the first food, beverage, or oral medication of the day is ingested.

Arch Fam Med. 1998;7:583-586

Alendronate sodium is a second-generation bisphosphonate, a class of synthetic compounds that bind to hydroxyapatite and inhibit bone resorption. In distinction to the earlier agents in this class, alendronate inhibits osteoclast-mediated bone resorption at doses that have little or no effect on osteoblast-mediated bone mineralization. Alendronate has been approved for the prevention and treatment of osteoporosis in postmenopausal women and treatment of Paget disease. In several large, randomized, placebo-controlled studies, its clinical efficacy has been established in osteoporosis, but there have been no direct comparative studies with the other antiresorptive agents that have been approved for treatment, estrogen and calcitonin. Also, synergistic effects with other agents have not been studied. Currently, the American Association of Clinical Endocrinologists recommends hormone replacement as the first line of therapy for both prophylaxis and treatment of osteoporosis in postmenopausal women. If there are contraindications or intolerance to hormone replacement therapy, alendronate may be considered an effective alternative (Table).3

INDICATIONS
The Food and Drug Administration–approved indications include prevention and treatment of osteoporosis in postmenopausal women and treatment of Paget disease. Diagnosis of osteoporosis may be confirmed by low bone mineral density (BMD), at least 2.5 SDs below the peak premenopausal mean, or a history of osteoporotic fracture. In Paget disease, treatment is indicated in patients with a serum alkaline phosphatase level at least 2 times the upper limit of normal, or in those who are clinically symptomatic or who are at risk for complications from their disease.

PHARMACOLOGY
Alendronate belongs to a class of synthetic compounds known as bisphosphonates, which adhere strongly to the hydroxyapatite crystal of bone. They differ from the endogenous pyrophosphonates (P-O-P) by the substitution of 2 carbon-phosphorus bonds (P-C-P) and the addition of methyl, sulphyl, or amine radicals on the middle carbon atom. Alendronate has a side chain amino group that makes it more selective for bone and approximately 1000 times more potent than etidronate disodium, a first-generation bisphosphonate, also approved for treatment.
of osteoporosis in postmenopausal women. Animal studies have shown that alendronate reduces the number of bone turnover sites and allows bone formation to exceed bone resorption at these remodeling sites. This results in a gradual increase in bone mass.

PHARMACOKINETICS

Absorption and Bioavailability

Compared with an intravenous reference dose, the oral bioavailability of a 10-mg tablet taken after an overnight fast and 2 hours before breakfast averaged less than 1%, with a significant variability within and between subjects. Coffee or orange juice taken with alendronate reduced bioavailability by approximately 60%. Absorption is negligible when the drug is taken up to 2 hours after breakfast. Use of calcium and other cations (eg, iron, zinc, magnesiu) may also interfere with absorption; thus, medications such as calcium or vitamin supplements should be taken at another time of day.

Distribution and Excretion

Elimination of alendronate appears to be exclusively through urinary excretion. After an intravenous infusion of 10 mg of alendronate sodium labeled with carbon 14, plasma concentrations decreased 95% within 6 hours and were undetectable beyond 12 hours. Approximately 40% to 50% was excreted in urine within 72 hours of treatment and another 15% was excreted slowly during an 8-month period. The rapid disappearance of alendronate in plasma with persistent urinary excretion suggests the slow redistribution of drug from another compartment, presumably bone. Since a portion of the initial dose is sequestered in bone and excreted very slowly, the terminal half-life is estimated to be greater than 10 years. However, the inhibition of bone resorption diminishes soon after the discontinuation of treatment. This suggests that as alendronate adsorbs to bone surfaces, it becomes buried under new bone formation and is no longer biologically active.

Efficacy

Treatment of Osteoporosis

The clinical efficacy of alendronate has been established in the treatment of osteoporosis in several large, randomized, placebo-controlled trials.

One study evaluated the effects of alendronate on BMD and incidence of fractures in 994 women (mean age, 64 years) with osteoporosis established by baseline lumbar BMD (at least 2.5 SDs below the mean value in premenopausal white women). Three doses of alendronate sodium were used: 5 mg/d, 10 mg/d, and 20 mg/d for 2 years, followed by 5 mg/d for 1 year. All the women received 500 mg of elemental calcium daily. At 3 years, the mean increase in BMD in the women receiving 10 mg/d of alendronate sodium compared with those receiving placebo was 8.8% in the spine, 5.9% in the femoral neck, 7.8% in the trochanter, and 2.5% in the total body. The 5-mg dose was less effective than the 10-mg dose, and the regimen of 20 mg followed by 5 mg was no better than the 10-mg/d dose. In fact, the efficacy of the 10-mg dose did not plateau during the course of the study, suggesting possible continued bone formation beyond the 3-year time frame of observation.

These increases in BMD were accompanied by a 48% reduction in the number of women with new vertebral fractures (3.2% in the alendronate group vs 6.2% in the placebo group). Total vertebral fracture rate was reduced by 63%, due to 4.2% of the placebo-treated women sustaining 2 or more fractures, compared with 0.6% of alendronate-treated women. The groups who appeared to derive most of the absolute benefit were women aged 65 years or older (2.6% vs 7.9% in the placebo group) and those with previous vertebral fractures (13.4% vs 19.1% in the placebo group).

There was also a trend toward a reduction in nonvertebral fractures in the alendronate group (7.5% alendronate vs 9.6% placebo). Hip fractures in particular occurred in only 3 women in the placebo group (0.8%) and 1 in the alendronate group (0.2%).

The Fracture Intervention Trial investigated the effect of alendronate on the incidence of vertebral and nonvertebral fractures in 2027 postmenopausal women (mean age, 71 years) with low femoral neck BMD and at least 1 vertebral fracture on baseline assessment. The initial dose of alendronate sodium was 5 mg/d, but when data from other studies indicated that 10 mg was the optimal dose, the participants were switched to the 10-mg dose at the 24-month follow-up visit. Women who had calcium intakes less than 1000 mg were given a supplement of 500 mg of calcium and 250 IU of cholecalciferol. At the end of 3 years, the increase in BMD in the alendronate group compared with the placebo group was 6.2% (lumbar spine), 4.7% (total hip), and 4.1% (femoral neck).

The risk of new radiographic vertebral fractures was 47% lower in the alendronate group than that in the placebo group (8.0% vs 15.0%). Most vertebral fractures produce minimal symptoms so that they escape recognition in actual clinical practice. Nevertheless, symptomatic vertebral fractures in this study were reduced to a similar extent (2.3% alendronate vs 5.0% placebo). The cumulative proportion of women with any clinical fracture was significantly lower in the alendronate group than in the placebo group (13.6% vs 18.2%), as were the subgroups of hip and wrist fractures (1.1% vs 2.2% and 2.2% vs 4.1%, respectively). The numbers of women with fractures at sites other than spine, hip, or wrist were no different in the alendronate and placebo groups.

Several questions pertaining to efficacy remain unanswered: how long treatment should be continued, benefit beyond 3 years, fracture risk when treatment is discontinued, effect of combining estrogen (with or without progestin) and alendronate, and effect of alendronate on osteoporosis in nonwhite women. Some of these questions are currently being investigated or will be answered by longer-term studies.

Treatment of Paget Disease

The clinical efficacy of alendronate also has been demonstrated in Paget disease. One study investigated the effect of alendronate on the incidence of vertebral and nonvertebral fractures in 2027 postmenopausal women (mean age, 71 years) with low femoral neck BMD and at least 1 vertebral fracture on baseline assessment. The initial dose of alendronate sodium was 5 mg/d, but when data from other studies indicated that 10 mg was the optimal dose, the participants were switched to the 10-mg dose at the 24-month follow-up visit. Women who had calcium intakes less than 1000 mg were given a supplement of 500 mg of calcium and 250 IU of cholecalciferol. At the end of 3 years, the increase in BMD in the alendronate group compared with the placebo group was 6.2% (lumbar spine), 4.7% (total hip), and 4.1% (femoral neck).

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disease.\textsuperscript{11} Response was defined as either normalization of levels of serum alkaline phosphatase or decrease from baseline by at least 60%. Eighty-five percent of those in the alendronate group responded, compared with 30% of those in the estrogen-progestin group and 0% in the placebo group. The 40-mg dose was more effective than 20 mg in suppressing the bone turnover indexes and maintaining clinical remission, but was not as well tolerated.

Prevention of Osteoporosis

The 2-year results of a study comparing placebo, alendronate (2.5 and 5 mg), and 2 estrogen-progestin regimens were recently presented.\textsuperscript{12} The study participants were healthy postmenopausal women aged 45 to 59 years with normal BMD (ie, within 2 SDs of average peak BMD). The placebo-treated patients lost BMD (-1.78% spine). The 2.5- and 5-mg alendronate groups, and the 2 estrogen-progestin groups, each gained BMD. A regimen of alendronate, 5 mg, and the 2 estrogen-progestin regimens each decreased markers of bone turnover. Adverse events in the placebo, 5-mg alendronate, and the estrogen-progestin groups resulted in discontinuation from the study in 2.2%, 2.0%, and 11.8% of subjects, respectively. Alendronate appears to be a promising alternative to estrogen for prevention of osteoporosis in women who cannot (or refuse to) take hormone replacement therapy.

ADVERSE EFFECTS

In a recent study,\textsuperscript{9} discontinuation of therapy due to clinical adverse reactions occurred in 4.1% of patients taking alendronate, 10 mg/d (n = 196), and 6.1% of patients taking placebo (n = 397). The most common side effects were abdominal pain (6.6% alendronate vs 4.8% placebo), nausea (3.6% vs 4.0%), dyspepsia (3.6% vs 3.5%), constipation (3.1% vs 1.8%), diarrhea (3.1% vs 1.8%), and musculoskeletal pain (4.1% vs 2.5%).

CONTRAINDICATIONS AND PRECAUTIONS

Alendronate is contraindicated in patients with the following: esophageal abnormalities that delay esophageal emptying, such as strictures or achalasia; inability to stand or sit upright for at least 30 minutes after taking medicine; hypersensitivity to any component of alendronate; and hypocalcemia.

Alendronate can cause esophagitis, esophageal ulcers, and esophageal erosions. Endoscopy has generally revealed lesions in the middle and/or distal portions of the esophagus, with relative sparing of the stomach and duodenum.\textsuperscript{13} The presumed mechanism is failed or delayed passage of the alendronate tablet through the esophagus, resulting in prolonged local mucosal exposure to the drug. In some cases, reflux of drug-containing gastric contents may have been responsible.

In the major trials of alendronate in osteoporosis, there was no evidence of a higher incidence of serious adverse esophageal effects than among those taking placebo.\textsuperscript{14} This discrepancy between clinical trial experience and postmarketing data is probably due to the controlled nature of clinical studies, in which participants have regularly scheduled follow-up visits and frequent reinforcement of dose instructions. It would appear then that strict adherence to the recommended dose instructions would minimize the risk for esophageal problems. On this basis, the manufacturer has explicitly advised that the drug should be taken, with a full glass of plain water only, when the patient is arising for the day, at least one-half hour before the first intake of food, beverage, or medication. Other beverages, including mineral water, may decrease absorption.

Alendronate is not recommended in patients with renal insufficiency with creatinine clearance less than 0.58 mL/s. No dosing adjustment is necessary for pa-
patients with mild to moderate renal insufficiency (creatinine clearance between 0.58 and 1.00 mL/s).

Calcium and vitamin D deficiencies should be corrected before initiating alendronate therapy. Because alendronate increases BMD, small, asymptomatic decreases in serum calcium and phosphate levels may occur. Thus, all patients taking alendronate should take supplemental calcium and vitamin D.

**DOSAGE, AVAILABILITY, AND COST**

Alendronate (Fosamax) is manufactured by Merck & Co Inc, West Point, Pa. The recommended dose for treatment of osteoporosis is 10 mg once a day, and for prevention, 5 mg once a day. For Paget disease, the recommended treatment regimen is 40 mg once a day for 6 months. The cost of Fosamax compared with other treatments for osteoporosis can be found in the Table.

**CONCLUSIONS**

In summary, alendronate is a bisphosphonate that inhibits bone resorption, which leads to decreased bone turnover sites and increased bone mass density. In osteoporosis, studies have demonstrated increased bone mass densities and a decreased fracture incidence in patients taking alendronate. In Paget disease of bone, alendronate decreases serum alkaline phosphatase levels. Because of the poor oral bioavailability especially when administered concurrently with food, patients must take alendronate with 180 to 240 mL of plain water 30 minutes before ingesting any food, medicine, or other beverages. Patients must also remain upright for at least 30 minutes, because alendronate can cause esophageal mucosal damage.

Accepted for publication July 16, 1998.

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