Bone Resorption Suppression and Related Agents Review

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FDA-Approved Indications

Drug	Manufacturer	Indication(s)
BISPHOSPHONATES		
alendronate (Fosamax®)	generic, Merck	• Treatment and prevention of osteoporosis in postmenopausal women • Treatment to increase bone mass in men with osteoporosis • Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent of 7.5 mg or greater of prednisone and who have low bone mineral density • Treatment of Paget's disease of bone in men and women
alendronate/ vitamin D (Fosamax Plus D™)	Merck	• Treatment of osteoporosis in postmenopausal women • Treatment to increase bone mass in men with osteoporosis
etidronate (Didronel®)	generic	• Treatment of Paget's disease of bone • Prevention and treatment of heterotopic ossification following total hip replacement or spinal cord injury
ibandronate (Boniva®)	Roche	• Treatment and prevention of osteoporosis in postmenopausal women
risedronate (Actonel®)	Procter & Gamble	• Treatment and prevention of osteoporosis in postmenopausal women • Treatment to increase bone mass in men with osteoporosis • Prevention and treatment of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent of 7.5 mg or greater of prednisone for chronic diseases • Treatment of Paget's disease of bone in men and women
risedronate/ calcium (Actonel with Calcium®)	Procter & Gamble	• Treatment and prevention of osteoporosis in postmenopausal women
CALCITONINS		
calcitonin-salmon (Miacalcin®)	generic, Novartis	• Treatment of postmenopausal osteoporosis in females greater than five years postmenopause with low bone mass. It should be reserved for patients who refuse or can not tolerate estrogens or in whom estrogens are contraindicated
calcitonin-salmon (Fortical®)	Upsher-Smith	• Treatment of postmenopausal osteoporosis in females greater than five years postmenopause with low bone mass.
OTHERS		
raloxifene (Evista®)	Lilly	• Treatment and prevention of osteoporosis in postmenopausal women • Reduction in risk of invasive breast cancer in postmenopausal women who either have osteoporosis or are at high risk for invasive breast cancer
teriparatide (Forteo™)	Lilly	• Treatment of osteoporosis in postmenopausal women who are at high risk for fractures • Increase of bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fractures

Overview

Osteoporosis is characterized by the deterioration of bone tissue and low bone mass. Ten million Americans have osteoporosis, and 34 million more have low bone mass, placing them at increased risk for this disease.[1] There are three categories of osteoporosis: postmenopausal, age-related, and secondary osteoporosis. Postmenopausal osteoporosis affects mainly trabecular bone in the decade after menopause as estrogen deficiency increases bone resorption more than bone formation. Age-related osteoporosis results from increased bone resorption that begins shortly after peak bone mass is obtained. Cortical and trabecular bone are both affected. Secondary osteoporosis is caused by medications (glucocorticoids, excess thyroid replacement, some antiepileptic drugs, and long-term heparin use) or diseases (hyperthyroidism, type 1 diabetes). Both types of bone are affected.

Non-pharmacologic prevention and treatment methods include social habit and dietary changes as well as exercise and fall prevention. Pharmacologic prevention and treatment focuses on limiting bone resorption. Each of the medication classes has a different mechanism of action and side effect profile. In the American Association of Clinical Endocrinologists guidelines for the prevention and treatment of postmenopausal osteoporosis (2003 update), the consensus opinion is that the first priority agents for pharmacotherapy include any drug that is FDA-approved for the prevention and/or treatment of osteoporosis.[2] The North American Menopause Society, in its 2006 position statement, says that selection of one therapy over another cannot be made on the basis of available clinical evidence due to a lack of head-to-head trials.[3] The 2008 National Osteoporosis Foundation (NOF) Clinician's Guide to Prevention and Treatment of Osteoporosis recognize all U.S. FDA-approved medications as possible options for the prevention and/or treatment of osteoporosis. The guide also state that the treatment agent of choice should be based on available clinical information in addition to intervention thresholds.[4]

Pharmacology

Bisphosphonates adsorb to bone apatite and are permanently incorporated into bone. Bone turnover and bone resorption are reduced as osteoclasts are unable to adhere to bone surfaces containing bisphosphonates. Ultimately, bisphosphonates inhibit osteoclasts and reduce bone turnover and resorption. Bisphosphonates include alendronate (Fosamax), etidronate (Didronel), ibandronate (Boniva), and risedronate (Actonel). The inclusion of vitamin D with alendronate (Fosamax Plus D) promotes calcium absorption. Risedronate with calcium (Actonel with Calcium) provides calcium supplementation in convenient packaging.

The hormone calcitonin is secreted in response to high serum calcium levels. Calcitonin receptors have been found on osteoclasts and renal cell membranes. Stimulation of these receptors by calcitonin-salmon (Miacalcin, Fortical) results in a decrease in osteoclast activity and a decrease in renal reabsorption of calcium and sodium. Bone formation may be augmented by increased osteoblastic activity.

The biological actions of raloxifene (Evista) are largely mediated through estrogen receptor binding. Binding results in activation of certain estrogenic pathways that act to decrease resorption of bone and reduce the biological markers of bone turnover. Raloxifene antagonizes estrogenic receptors in the uterine and breast tissue and also decreases total and low density lipoprotein (LDL) cholesterol.

Parathyroid hormone can increase bone resorption, but it is anabolic if used daily. Anabolic activity may result in decreased osteoblast apoptosis and increased bone formation from the longer-lived osteoblasts. Teriparatide (Forteo) stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity.

Pharmacokinetics

Drug	Bioavailability (%)	Half-Life	Metabolism	Excretion (%)
BISPHOSPHONATES				
alendronate (Fosamax)[5]	0.64	>10 yrs	No metabolism	Renal: 50
vitamin D* (Fosamax Plus D)[6]	--	14 hrs	Liver hydroxylation to active form; metabolized by kidneys	Renal and fecal
etidronate (Didronel)[7]	3	1-6 hrs	No metabolism	Renal: 50
ibandronate (Boniva)[8]	0.6	37-157 hrs	No metabolism	Fecal
risedronate (Actonel)[9]	0.63	20 days	No metabolism	Renal: 50
calcium (Actonel with Calcium)[10]	--	--	--	Fecal
CALCITONINS				
calcitonin-salmon (Miacalcin, Fortical)[11,12]	3	43 mins	--	--
OTHERS				
raloxifene (Evista)[13]	2	27.7 hrs	Three metabolites	Fecal
teriparatide (Forteo)[14]	95	1 hr	--	--

- Alendronate pharmacokinetics are not altered by the addition of vitamin D.

Contraindications/Warnings[15,16,17,18,19,20,21,22]

Chronic, severe musculoskeletal pain has been reported in patients taking bisphosphonates. Patients may experience pain symptoms at any time after treatment initiation with a bisphosphonate. Upon discontinuation of the bisphosphonate, relief of pain symptoms has come in the form of slow or incomplete symptom resolution to complete relief. The FDA continues to investigate this possible association. In the interim, if a patient reports musculoskeletal pain while on treatment with a bisphosphonate, the NOF recommends that the bisphosponate be discontinued until the pain symptoms resolve.

Teriparatide (Forteo) has a black box warning indicating that osteosarcoma was seen in both male and female rats. The osteosarcoma was dependent on dose and treatment duration. Teriparatide should not be used in patients who are at increased risk of osteosarcoma, including those with Paget's disease, open epiphyses, previous recipients of radiation of the bone, or those with unexplained elevations of alkaline phosphatase.

Bisphosphonates are generally contraindicated in the following conditions: abnormalities of the esophagus which delay esophageal emptying, inability to stand or sit upright for 30 to 60 minutes, and hypocalcemia.

Raloxifene (Evista) is contraindicated in lactating and pregnant women as well as women who may become pregnant and women with active or a history of venous thromboembolism. There are black box warnings for the increased risk of venous thromboembolism and death from stroke.

Drug Interactions[23,24,25,26,27]

Raloxifene (Evista) should not be used concomitantly with systemic estrogens. As this agent is highly protein bound, raloxifene should be used with caution with other highly protein-bound medications, such as diazepam.

Concomitant use of bisphosphonates with hormone replacement therapy (HRT) in women shows a greater degree of bone turnover suppression than with either HRT or a bisphosphonate alone.

Calcium supplements and antacids, as well as other oral medications, may interfere with the absorption of bisphosphonates. Patients should not take other medications until the 30 to 60 minute period following administration is completed.

The incidence of upper gastrointestinal adverse events is higher in patients taking aspirin or NSAIDs concomitantly with bisphosphonates. Administration with a proton pump inhibitor or H_2-blocker may decrease the incidence.

Cholestyramine, and possibly other bile acid resins, can cause a decrease in the absorption of raloxifene (Evista), thus concomitant use of these agents is not recommended.

Adverse Effects

Drug	Abd. pain	Nausea	Dyspepsia	Constipation	Diarrhea	Flatulence	Musculoskeletal pain	Headache
BISPHOSPHONATES								
alendronate (Fosamax)[28] 5-10 mg daily	1.5-6.6	1.1-3.6	1.1-3.6	0-3.1	0.6-3.1	0.2-4.1	0.4-4.1	0.2-2.6
alendronate (Fosamax)[29] 35 mg once-weekly	2.2	1.4	1.7	0.3	0.6	<1	2.2	<1
alendronate (Fosamax)[30] 70 mg once-weekly	3.7	1.9	2.7	0.8	<1	0.4	2.9	<1
etidronate (Didronel)[31]	nr	7-30	nr	nr	7-30	nr	reported	reported
ibandronate (Boniva)[32] 2.5 mg daily	5.3	4.8	7.1	2.5	4.1	nr	nr	4.1
ibandronate (Boniva)[33] 150 mg once-monthly	7.8	5.1	5.6	4.0	5.1	nr	nr	3.3
risedronate (Actonel)[34] 5 mg daily	7.3-11.6	8.5-10.9	2.5-6.9	12.5	6.3-10.6	3.3-4.6	11.5-23.7	7.3
risedronate (Actonel)[35] 35 mg once-weekly	7.6	6.2	7.6	12.2	4.9	3.1	14.2	7.2
risedronate (Actonel)[36] 75 mg two days/month	nr	nr	nr	nr	nr	nr	nr	nr
risedronate (Actonel)[37] 150 mg once/month	nr	nr	nr	nr	8.2	nr	nr	nr
CALCITONINS								
calcitonin-salmon (Miacalcin)[38]	1-3	1-3	1-3	1-3	1-3	<1	nr	3.2 (4.6)
calcitonin-salmon (Fortical)[39]	1-3	1-3	1-3	1-3	1-3	<1	nr	3.2 (4.6)
OTHERS								
raloxifene (Evista)[40] 60 mg daily	6.6	8.3-8.8	5.9	nr	7.2	1.6-3.1	10.7-15.5	9.2
teriparatide (Forteo)[41]	nr	8.5	5.2	5.4	5.1	nr	nr	7.5

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative. nr = not reported.

Although there has been no study of adverse events with Fosamax Plus D, in one study with 682 women and 35 men, a combination of alendronate and vitamin D over 15 weeks had a safety profile similar to alendronate 70 mg once weekly. [42]

Other

Etidronate (Didronel) has an incidence of diarrhea and nausea in seven to 30 percent of patients.[43]

Bisphosphonates have had reports of bone, joint, and muscle pain as well as osteonecrosis of the jaw.[44,45,46]

Other common adverse events reported with raloxifene (Evista) include leg cramps, hot flashes, varicose veins, peripheral edema, and vaginal hemorrhage.[47]

Calcitonin-salmon (Miacalcin, Fortical) causes rhinitis (12 percent), epistaxis (3.5 percent), and other bothersome effects of the nose. Periodic nasal examinations are recommended during nasal calcitonin-salmon therapy.[48,49]

Adverse effects reported with teriparatide (Forteo) included hypertension (7.1 percent), angina pectoris (2.5 percent), syncope (2.6 percent), arthralgia (10.1 percent), dizziness (eight percent), depression (4.1 percent), insomnia (4.3 percent), and sweating (2.2 percent). Transition elevation of serum calcium has been seen in both women and men.[50]

Special Populations

Pediatrics

These products are not FDA-approved for use in the pediatric population. There are limited data available studying the use of these products in pediatric disorders such as osteogenesis imperfecta, but large, properly-designed studies have not been conducted.

Pregnancy

All products in this class are in Pregnancy Category C, with the exception of raloxifene (Evista), which is Pregnancy Category X.[51]

Hepatic Impairment

Raloxifene (Evista) should be used with caution in patients with hepatic impairment.[52]

Renal Impairment

The use of bisphosphonates is not recommended in patients with severe renal dysfunction.

Dosages

Drug	Treatment of osteoporosis in postmenopausal women	Prevention of osteoporosis in postmenopausal women	Paget's disease	Availability	Comments
BISPHOSPHONATES					
alendronate (Fosamax)	10 mg per day or 70 mg once per week	5 mg per day or 35 mg once per week	40 mg per day for 6 months	5, 10, 35, 40, 70 mg tablets; 70 mg/75 mL bottle	not recommended if CLcr <35 mL/min
alendronate/ vitamin D (Fosamax Plus D)	70 mg/2,800 IU or 70 mg/5,600 IU weekly	--	--	70 mg/ 2,800 IU, 70 mg/ 5,600 IU tablets	not recommended if CLcr <35 mL/min
etidronate (Didronel)	--	--	5-10 mg/kg/day up to 6 months or 11-20 mg/kg/day up to 3 months	200, 400 mg tablets	dose should be reduced in renal insufficiency
ibandronate (Boniva)	2.5 mg per day or 150 mg per month or 3mg given via injection every 3 months	2.5 mg per day or 150 mg per month	--	2.5, 150 mg tablets, 3mg/3mL prefilled syringe	not recommended if CLcr <30 mL/min
risedronate (Actonel)	5 mg per day or 35 mg once per week or 75 mg for 2 consecutive days every month or 150 mg once a month	5 mg per day or 35 mg once per week or 75 mg for 2 consecutive days every month or 150 mg once a month	30 mg per day for 2 months	5, 30, 35, 75, 150 mg tablets	not recommended if CLcr <30 mL/min
risedronate/ calcium (Actonel with Calcium)	35 mg risedronate once weekly on day one of the seven day treatment cycle, and 1,250 mg calcium carbonate on days two through seven	35 mg risedronate once weekly on day one of the seven day treatment cycle, and 1,250 mg calcium carbonate on days two through seven	--	35 mg/1,250 mg in a 28-day package	not recommended if CLcr <30 mL/min
CALCITONINS					
calcitonin-salmon (Miacalcin)	200 IU intranasally per day, alternating nostrils daily	--	--	2 mL (14 dose), 3.7 mL (30 dose) bottles	refrigerate; may store at room temperature for 30 days
calcitonin-salmon (Fortical)	200 IU intranasally per day, alternating nostrils daily	--	--	3.7 mL (30 dose) bottle	refrigerate; may store at room temperature for 30 days
OTHERS					
raloxifene (Evista)	60 mg per day	60 mg per day	--	60 mg tablets	Not recommended in moderate or severe renal impairment
teriparatide (Forteo)	20 mcg SC per day	--	--	750 mcg/3 mL prefilled pen	store in refrigerator; discard 28 days after first use

Other Dosages

Alendronate (Fosamax) to increase bone mass in men: 10 mg per day or 70 mg once weekly; for treatment of glucocorticoid induced osteoporosis: 5 mg per day (except for postmenopausal women not receiving estrogen, for whom the recommended dosage is 10 mg per day).

Alendronate/Vitamin D (Fosamax Plus D) to increase bone mass in men: 70 mg/2,800 IU or 70 mg/5,600 IU once weekly.

Etidronate (Didronel) for Heterotrophic Ossification: 20mg/kg/day for two weeks then 10 mg/kg/day for ten weeks for spinal cord injury; for hip replacement, 20 mg/kg/day for one month prior to surgery followed by 20mg/kg/day for three months postoperatively.

Risedronate (Actonel) for treatment of glucocorticoid induced osteoporosis: 5 mg per day; to increase bone mass in men with osteoporosis: 35 mg once weekly.

Raloxifene (Evista) dosing is 60 mg daily for all indications.

Teriparatide (Forteo) to treat osteoporosis in men: 20 mcg SC once daily.

Alendronate and risedronate must be taken at least one-half hour before the first food, beverage, or medication of the day with plain water only. Patients should not lie down for at least 30 minutes after taking the medication. Ibandronate must be taken at least one hour before the first food, beverage, or medication of the day with plain water, and patients should not lie down for at least 60 minutes after taking the medication.

All regimens should include an adequate intake of calcium and vitamin D.

Clinical Trials

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

alendronate (Fosamax) and placebo

Two double-blind, multicenter studies were conducted enrolling postmenopausal women who were 45 to 80 years of age with osteoporosis [bone mineral density (BMD) at least 2.5 standard deviations below the mean value in premenopausal white women].[53] The women were randomized to receive placebo or 5, 10, or 20 mg of alendronate per day for two years. During the third year, women continued with open-label therapy with the 20 mg per day group changing to 5 mg per day. All women also received 500 mg of calcium daily. A total of 909 women completed at least one year of the study. There were significant increases in the BMD of the spine, femoral neck, trochanter, and total body at 36 months in all three alendronate groups. The 10 mg dose was significantly more effective than the 5 mg dose and at two years, was as effective as the 20 mg dose. During the study, 6.2 percent of the placebo group had at least one new vertebral fracture compared with 3.2 percent of the alendronate-treated females (p=0.03).

In the Fracture Intervention Trial (FIT), 4,432 women with a femoral neck BMD of 0.68 g/cm^2 or less were randomized in a double-blind manner to receive alendronate 5 mg per day for two years followed by 10 mg per day for two years or placebo.[54] Alendronate increased BMD at all sites studied and reduced clinical fractures from 312 in the placebo group to 272 in the intervention group. However, the clinical fracture reduction was not significant.

A randomized, double-blind trial enrolled 1,099 postmenopausal women who had received alendronate treatment in FIT for a mean of five years. These patients were again randomized to alendronate, 5 or 10 mg daily, or placebo for an additional five years. The primary outcome measure was total hip BMD; secondary measures were BMD at other sites and biochemical markers of bone remodeling. Patients who switched to placebo for five years had a decline in BMD at the total hip (-2.4 percent; p<0.001) and spine (-3.7 percent; p<0.001), but mean levels remained at or above pretreatment levels 10 years earlier. After five years, the cumulative risk of nonvertebral fractures was not significantly different between those continuing and discontinuing alendronate (RR, 1.00; 95% CI, 0.76-1.32). Among those who continued, there was a significantly lower risk of clinically recognized vertebral fractures (RR, 0.45; 95% CI, 0.24-0.85) but no significant reduction in morphometric vertebral fractures.

In a one-year, double-blind study, 1,258 osteoporotic women were randomized to receive alendronate 10 mg daily, 35 mg twice weekly or 70 mg once weekly.[55] The percent increases for BMD of the lumbar spine at month 12 were 5.4, 5.2, and 5.1 for the three dosing regimens, respectively. Upper gastrointestinal adverse experiences occurred in 23.5 percent, 23.8 percent and 22.4 percent of patients in the daily, twice-weekly, and once-weekly treatment groups, respectively.

In a one-year, double-blind, multicenter study of postmenopausal women aged 40 to 70 years, 362 patients were randomized to alendronate 35 mg once weekly, and 361 patients received alendronate 5 mg once daily.[56] Lumbar spine BMD at 12 months increased to the same degree in both groups. Both treatments were well tolerated.

A multicenter, international, randomized, blinded, 12-month study was conducted to assess the effect of alendronate on BMD in women who had recently discontinued HRT.[57] One hundred forty-four postmenopausal women were randomized to receive either a daily dose of 10 mg alendronate or matching placebo. A high rate of bone loss was observed in the first 12 to 15 months after discontinuation of HRT. Alendronate increased or maintained both spine and hip BMD and prevented the increase in bone resorption seen with withdrawal of HRT in this population.

alendronate (Fosamax) and raloxifene (Evista)

A randomized, double-masked, double-dummy multicenter international study was done to compare the efficacy and tolerability of alendronate to raloxifene in postmenopausal women with low-bone density.[58] A total of 487 postmenopausal women with low bone density, based on BMD of the lumbar spine or hip (T-score $\leq$ -2.0), received either alendronate 70 mg once weekly and daily placebo identical to raloxifene or raloxifene 60 mg daily and weekly placebo identical to alendronate for 12 months. Alendronate demonstrated substantially greater increases in BMD than raloxifene at both lumbar spine and hip sites at 12 months. Lumbar spine BMD increased 4.8 percent with alendronate compared to 2.2 percent with raloxifene ($p<0.001$). The increase in total hip BMD was 2.3 percent with alendronate and 0.8 percent with raloxifene ($p<0.001$). The proportion of patients reporting vasomotor events was significantly higher with raloxifene (9.5 percent) than with alendronate (3.7 percent, $p=0.010$). The proportion of patients reporting gastrointestinal events was similar between groups. In postmenopausal women with low bone density, improvements in BMD and markers of bone turnover were substantially greater during treatment with alendronate compared to raloxifene.

To compare the efficacy and tolerability of once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis, a 12-month, randomized, double-blind study enrolled 456 patients.[59] Over 12 months, alendronate produced a significantly greater increase in lumbar spine BMD than raloxifene (4.4 versus 1.9 percent, $p<0.001$). The percentage of women with an increase in lumbar spine BMD (94 versus 75 percent; $p<0.001$) and more than a three percent increase (66 versus 38 percent; $p<0.001$) was significantly greater with alendronate than raloxifene. Total hip and trochanter BMD increases were also significantly greater ($p\leq0.001$) with alendronate. No significant differences in the incidence of upper gastrointestinal or vasomotor adverse experiences were seen.

alendronate (Fosamax) and risedronate (Actonel)

A total of 515 postmenopausal women received risedronate 5 mg or alendronate 10 mg daily for two weeks.[60] At baseline and days eight and 15, subjects underwent endoscopy and evaluator-blinded assessment of the esophageal, gastric, and duodenal mucosa. Gastric ulcers were seen in 4.1 percent of risedronate-treated patients and in 13.2 percent of the alendronate group. Esophageal ulcers were noted in three subjects in the alendronate group compared to none in the risedronate group. Duodenal ulcers were found in one patient in the alendronate-treated group and in two patients in the risedronate group.

In a similarly conducted study, 318 subjects received risedronate 5 mg and 317 received alendronate 10 mg daily for 14 days.[61] Overall, gastric ulcers greater than 3 mm were observed in 18 (six percent) of 300 evaluated subjects in the risedronate group and 36 (12.1 percent) of 297 in the alendronate group during treatment ($p=0.013$). Mean gastric endoscopy scores at days eight and 15 were significantly lower in the risedronate group than in the alendronate group ($p<0.001$). Mean esophageal and duodenal endoscopy scores were similar in the two groups at days eight and 15. Upper GI adverse events were reported by 18 (5.7 percent) subjects in the risedronate group (19 events) and 28 (8.8 percent) subjects in the alendronate group (32 events).

In a multicenter, double-blind trial, 235 men and postmenopausal women were randomized to receive 28 days of alendronate 40 mg per day, risedronate 30 mg per day, placebo, or placebo with aspirin 650 mg four times a day for the last seven days.[62] Endoscopy showed alendronate- and risedronate-treated patients with comparable mean gastric and duodenal erosion scores that were significantly lower than those of the aspirin group. Gastric ulcers and/or large numbers of

gastric erosions occurred in approximately three percent of alendronate and risedronate patients versus 60 percent with aspirin.

In FACT, a total of 1,053 patients were randomized in a double-blind study to alendronate 70 mg once weekly (n=520) or risedronate 35 mg once weekly (n=533) taken in the morning after fasting.[63] Greater increases in hip trochanter BMD were seen with alendronate (3.4 percent) than risedronate (2.1 percent) at 12 months ($p<0.001$) as well as six months ($p<0.001$). Significant gains in BMD were greater with alendronate at all BMD sites measured (12-month difference: total hip, one percent; femoral neck, 0.7 percent; lumbar spine, 1.2 percent). No significant differences were seen between treatment groups in the incidence of upper gastrointestinal adverse events or those causing discontinuation.

A randomized, double-blind, one-year extension of FACT compared changes in BMD, bone turnover, and upper gastrointestinal tolerability over two years of treatment.[64] Of the 1,053 women who completed one year of treatment, 833 postmenopausal women with low BMD entered the extension, continuing their same treatment allocation. Alendronate produced greater increases from baseline in BMD at 24 months than did risedronate at the trochanter (alendronate 4.6 percent; risedronate 2.5 percent, $p<0.001$), as well as at all other BMD sites. Fewer alendronate patients had measured decreases of three percent or more at all BMD sites. Significantly greater reductions in all biochemical markers of bone turnover occurred with alendronate, compared with risedronate. No differences were seen in occurrence or discontinuations due to upper gastrointestinal adverse effects. The manufacturer of alendronate supported the study.

A three-month, randomized, double-blind, placebo-controlled study with a double-blind extension to 12 months enrolled 549 postmenopausal women who were 60 years of age or older.[65] Patients received alendronate 70 mg once weekly or risedronate 5 mg daily. Over three months, alendronate produced a significantly greater mean reduction in biochemical markers of bone turnover than did risedronate, which was maintained at 12 months. Alendronate produced a significantly greater mean BMD increase than did risedronate at six months, and it was maintained at 12 months at the lumbar spine (4.8 versus 2.8 percent, $p<0.001$) and total hip (2.7 versus 0.9 percent, $p<0.001$), as well as at the trochanter and femoral neck. Tolerability was generally similar among alendronate, risedronate, and placebo, and the incidence of adverse events was similar in both active treatment groups.

<u>alendronate with vitamin D (Fosamax Plus D) and alendronate (Fosamax)</u>

In a 15-week study, 717 men and postmenopausal women with osteoporosis were randomized to receive weekly alendronate/vitamin D 70 mg/2,800 IU tablets or weekly alendronate 70 mg.[66] Patients who were vitamin D deficient at baseline were excluded. Treatment with alendronate/vitamin D resulted in a smaller reduction in serum calcium levels (-0.9 versus -1.4 percent) as well as a significantly smaller increase in parathyroid hormone levels when compared to alendronate alone (14 versus 24 percent).

<u>calcitonin salmon (Miacalcin) and placebo</u>

For five years, 1,255 randomized, postmenopausal women with osteoporosis received salmon calcitonin nasal (100, 200, or 400 IU) or placebo daily in a double-blind manner.[67] The 200 IU dose of salmon calcitonin nasal spray significantly reduced the risk of new vertebral fractures by 33 percent compared with placebo ($p=0.03$). Lumbar spine BMD increased significantly from baseline (one percent to 1.5 percent, $p<0.01$) in all active treatment groups.

ibandronate (Boniva) and placebo

In total, 653 women (mean BMD T-score > -2.5 at the lumbar spine) who had been postmenopausal for at least one year were enrolled in a multicenter, double-blind, randomized, placebo-controlled, Phase II/III study to receive calcium (500 mg daily) plus either placebo (n=162) or ibandronate 0.5 mg (n=162), 1 mg (n=166), or 2.5 mg (n=163) as daily treatment for two years.[68] After two years, daily ibandronate produced a dose-related and sustained maintenance or increase in BMD at the lumbar spine and hip (total hip, femoral neck, trochanter), together with a dose-related reduction in the rate of bone turnover. The greatest increases in spinal and hip BMD were observed with the 2.5 mg dose, which produced statistically significant BMD gains compared with placebo at six months and all subsequent time-points (3.1 and 1.8 percent increase in lumbar spine and total hip BMD, respectively, versus placebo; $p \leq 0.0001$ after 24 months). Ibandronate was well tolerated with an incidence of upper gastrointestinal adverse events similar to placebo.

A randomized, double-blind, placebo-controlled, parallel-group, Phase III study enrolled 2,946 postmenopausal women with a BMD T score = - 2.0 at the lumbar spine in at least one vertebra and one to four prevalent vertebral fractures.[69] Patients received placebo or ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every three months. Daily and intermittent ibandronate significantly reduced the risk of new vertebral fractures by 62 percent (p=0.0001) and 50 percent (p=0.0006), respectively, versus placebo. Significant and progressive increases in lumbar spine and hip BMD, normalization of bone turnover, and significantly less height loss than in the placebo group were also observed for both ibandronate regimens. The overall population was at low risk for osteoporotic fractures. Consequently, the incidence of nonvertebral fractures was similar between the ibandronate and placebo groups after three years (9.1, 8.9, and 8.2 percent in the daily, intermittent, and placebo groups, respectively). Ibandronate was well tolerated.

A total of 1,609 women with postmenopausal osteoporosis were assigned to one of four oral ibandronate regimens, 2.5 mg daily, 50 mg/50 mg monthly (single doses, consecutive days), 100 mg monthly, or 150 mg monthly, in a two-year, randomized, double-blind, Phase III, non-inferiority trial.[70] After one year, lumbar spine BMD increased by 3.9, 4.3, 4.1, and 4.9 percent in the 2.5, 50/50, 100, and 150 mg arms, respectively. All monthly regimens were proven non-inferior to the daily regimen in increasing lumbar BMD, while the 150 mg regimen was superior. All arms of the study produced similar hip BMD gains, and all arms were similarly well tolerated.

ibandronate (Boniva) and alendronate (Fosamax)

A 12-month, randomized, multinational, multicenter, double-blind, double-dummy, parallel-group, non-inferiority trial enrolled postmenopausal women with mean lumbar spine (L2-L4) BMD T-score < -2.5 and ≥ -5.0.[71] Patients received either ibandronate 150 mg once monthly or alendronate 70 mg once weekly. The primary efficacy endpoints were 12-month percent change from baseline in mean lumbar spine and total hip BMD, while percent changes from baseline in trochanter and femoral neck BMD were also evaluated. Once-monthly ibandronate was considered non-inferior to weekly alendronate if the lower boundary of the one-sided 97.5% confidence interval (CI) (or two-sided 95% CI) was ≥ -1.41 percent for lumbar spine and ≥ -0.87 percent for total hip. The mean relative 12-month changes were 5.1 percent and 5.8 percent (95% CI, -1.13 to -0.23) in lumbar spine and 2.9 percent and 3.0 percent (95% CI, -0.38 to 0.18) in total hip BMD with once-monthly ibandronate and weekly alendronate, respectively. Therefore, once-monthly ibandronate was shown to be clinically comparable to weekly alendronate at increasing BMD after 12 months in both the lumbar spine and total hip.

raloxifene (Evista) and placebo

To evaluate the three-year effects of raloxifene treatment on BMD, 1,145 postmenopausal women were enrolled in a randomized, double-blind trial.[72] They received raloxifene 30, 60, or 150 mg or placebo daily. Lumbar spine BMD changed from baseline to 36 months as follows: placebo, -1.32 percent; raloxifene 30 mg, +0.71 percent; raloxifene 60 mg, +1.28 percent; and raloxifene 150 mg, +1.2 percent. Comparable BMD changes were observed in the hip and total body. The significant adverse effect of active treatment was hot flashes (25 percent in the raloxifene 60 mg group versus 18 percent in the placebo group).

In a randomized double-blind trial, 7,705 women who had osteoporosis received raloxifene 60 or 120 mg per day or placebo.[73] Women receiving raloxifene had fewer new vertebral fractures. One hundred seventeen women had two or more new vertebral fractures. Compared to placebo, BMD increased after 36 months by 2.1 and 2.6 percent at the femoral neck and spine, respectively, in the 60 mg raloxifene group and by 2.4 and 2.7 percent at the femoral neck and spine, respectively, in the 120 mg raloxifene group (all $p<0.001$). Thromboembolic events were reported more frequently in the raloxifene groups (one percent for each active treatment group compared to 0.3 percent for the placebo group). In an extension of the study, placebo-treated women continued with placebo (n=1,286), but those previously given raloxifene 60 or 120 mg daily received raloxifene 60 mg daily (n=2,725).[74] As a secondary endpoint, new non-vertebral fractures were analyzed in 4,011 postmenopausal women after eight years. The risk of at least one new non-vertebral fracture was similar in the placebo (22.9 percent) and raloxifene (22.8 percent) groups, and the incidence of at least one new non-vertebral fracture at six major sites (clavicle, humerus, wrist, pelvis, hip, lower leg) was 17.5 percent in both groups. The differences in mean lumbar spine and femoral neck BMD with raloxifene were 1.7 percent ($p=0.30$) and 2.4 percent ($p=0.045$), respectively, from placebo. Compared with baseline, raloxifene treatment significantly increased lumbar spine (4.3 percent from baseline, 2.2 percent from placebo) and femoral neck BMD (1.9 percent from baseline, three percent from placebo).

risedronate (Actonel) and placebo

A randomized, double-blind, placebo-controlled trial of 2,458 postmenopausal women younger than 85 years with at least one vertebral fracture at baseline were randomly assigned to receive oral treatment for three years with risedronate 2.5 or 5 mg daily or placebo.[75] The risedronate 2.5 mg daily arm was discontinued after one year; the placebo (450 subjects) and risedronate 5 mg daily (489 subjects) arms completed all three years of the trial. Treatment with 5 mg daily of risedronate significantly reduced the cumulative incidence of new vertebral fractures over three years (11.3 versus 16.3 percent) versus placebo ($p=0.003$). The cumulative incidence of nonvertebral fractures over three years was significantly reduced (5.2 versus 8.4 percent) versus placebo. BMD increased significantly compared with placebo at the lumbar spine (5.4 versus 1.1 percent), femoral neck (1.6 versus -1.2 percent), femoral trochanter (3.3 versus -0.7 percent), and midshaft of the radius (0.2 versus -1.4 percent).

In a two-protocol study, 9,331 women were randomized to evaluate the effects of risedronate 2.5 mg, 5 mg, or matching placebo given daily for three years to prevent hip fractures.[76] All women also received supplemental calcium carbonate. The women were divided into two groups: 70 to 79 years of age with osteoporosis and 80 years of age or older with one or more clinical risk factors for hip fracture. The mean duration of therapy was two years, and 64 percent of patients had complete follow-up data. There was a significant decrease in the risk of hip fracture in all patients who were on risedronate versus placebo treatment (2.8 percent compared to 3.9 percent, $p=0.02$). Patients in the 80 years of age and older group did not show a significant decrease in risk of hip fracture when treated with risedronate.

In order to determine the effects of five years of risedronate treatment, the authors extended a three-year, placebo-controlled vertebral fracture study in osteoporotic women for an additional two years.[77] Women who entered the extension study continued to receive 5 mg risedronate or placebo according to the original randomization, with maintenance of blinding. The risk of new vertebral fractures was significantly reduced with risedronate treatment in years four and five. Significant decreases in markers of bone turnover observed in the first three years were similarly maintained in the next two years of treatment. Increases in spine and hip BMD that occurred in the risedronate group during the first three years were maintained or increased with a further two years of treatment.

In an 18-month, randomized, double-blind trial, 280 male patients 65 years or older who were post-stroke received a risedronate 2.5 mg daily (n=140) or placebo (n=140).[78] Ten patients sustained hip fractures in the placebo group, and two hip fractures occurred in the risedronate group. The relative risk of a hip fracture was 0.19 (95% CI, 0.04-0.89). Bone mineral density increased by 2.5 percent in the risedronate group and decreased by 3.5 percent in the placebo group ($p<0.001$).

<u>risedronate (Actonel) and etidronate (Didronel)</u>

Patients with Paget's disease of bone received risedronate 30 mg daily for two months (n=62) or etidronate 400 mg daily for six months (n=61) in a prospective, randomized, double-blind study.[79] Serum alkaline phosphatase, serum bone-specific alkaline phosphatase, and urinary deoxypyridinoline concentrations were monitored for 12 to 18 months. Serum alkaline phosphatase concentration normalized by month 12 in 73 percent of risedronate-treated patients, compared with 15 percent of those receiving etidronate ($p<0.001$). Median time to normalization was 91 days for risedronate-treated patients and greater than 360 days for etidronate-treated patients ($p<0.001$); relapse rates were three percent in the risedronate group and 15 percent in the etidronate group ($p<0.05$). At month 18, 53 percent of the risedronate group and 14 percent of the etidronate group remained in biochemical remission. Urinary deoxypyridinoline and serum bone-specific alkaline phosphatase levels normalized in significantly more risedronate patients than etidronate patients, as well. Reductions in pain were statistically significant in the risedronate group but not in the etidronate group. Both drugs were well tolerated.

<u>teriparatide (Forteo) and placebo</u>

A total of 1,637 postmenopausal women with prior vertebral fractures were randomized to receive parathyroid hormone 20 or 40 mcg subcutaneously (SC) or placebo daily for a median duration of 21 months.[80] In the blinded trial, new vertebral fractures occurred in five, four, and 14 percent of the 20 mcg and 40 mcg parathyroid hormone compared to placebo patients, respectively. BMD was increased by nine and 13 more percentage points in the lumbar spine and by three and six more percentage points in the femoral neck for the 20 mcg and 40 mcg parathyroid hormone groups compared to the placebo groups. Occasional nausea and headache occurred in the parathyroid hormone patients. The 40 mcg dose increased BMD more than the 20 mcg dose but had similar effects on the risk of fracture and was more likely to have side effects.

<u>teriparatide (Forteo) and alendronate (Fosamax)</u>

In a double-blind study of 146 postmenopausal women with osteoporosis, 73 women were randomized to once daily SC injections of teriparatide 40 mcg, and 73 women were randomized to once daily alendronate 10 mg for 14 months.[81] At three months, teriparatide increased lumbar spine BMD by 12.2 percent, and alendronate increased BMD by 5.6 percent ($p<0.001$). Teriparatide also increased femoral neck BMD and total body bone mineral significantly more than did alendronate ($p\leq0.05$). Additionally, nonvertebral fracture incidence was significantly

lower in the teriparatide group ($p \leq 0.05$). Both treatments were well tolerated despite transient mild asymptomatic hypercalcemia with teriparatide treatment.

A randomized and blinded clinical trial involving 238 postmenopausal women with low hip or spine BMD was carried out at four centers.[82] In the study, the women were given a daily regimen of PTH, alendronate, or a combination of the two. After 12 months, results showed no significant benefit to combining treatments.

In an 18-month, randomized, parallel, double-blind study, 203 postmenopausal women with osteoporosis received teriparatide 20 mcg or alendronate 10 mg.[83] Teriparatide significantly increased markers of bone turnover that peaked at six months (serum procollagen type I N-terminal propeptide, 218 percent and urinary N-telopeptide corrected for creatinine, 58 percent; $p<0.001$); alendronate significantly decreased the markers at six months (-67 percent and -72 percent, respectively; $p<0.001$). At 18 months, areal and volumetric spine BMDs were significantly higher with teriparatide than with alendronate (10.3 percent versus 5.5 percent [$p<0.001$] and 19 percent versus 3.8 percent [$p<0.01$], respectively).

teriparatide (Forteo) and raloxifene (Evista)

A six-month randomized, double-blind trial comparing teriparatide plus raloxifene (n=69) versus teriparatide plus placebo (n=68) was conducted in postmenopausal women with osteoporosis.[84] Bone formation increased similarly in both treatment groups. However, the increase in bone resorption in the combination group was significantly smaller than in the teriparatide-alone group ($p=0.015$). Lumbar spine BMD significantly increased 5.19 percent from baseline in the teriparatide-alone group, and 6.19 percent in the combination group. Also, femoral neck and total hip BMD significantly increased in the combination group, and the increase in total hip BMD was significantly greater than in the teriparatide-alone group ($p=0.04$). The safety profile of combination therapy was similar to teriparatide alone.

Adherence to Treatment Regimen

Daily dosing versus weekly dosing

Claims data for 30 health plans between 1997 and 2002 were used to identify postmenopausal women with osteoporosis who had been newly prescribed a once weekly bisphosphonate (alendronate 35 mg or 70 mg; n=731) or a once daily bisphosphonate (alendronate 5 mg or 10 mg or risedronate 5 mg; n=2010).[85] Data was examined for twelve months from the date of the initial prescription in an attempt to compare weekly and daily bisphosphonate treatment regimens relative to compliance and persistence. Medication possession ratios (MRPs) were used to measure refill compliance during follow up. Patients treated with a weekly bisphosphonate were found to have significantly higher medication compliance as compared to patients taking daily treatment (69.2 percent versus 57.6 percent MRP, $p=0.0001$). Those patients on weekly treatment were also found to persist with treatment significantly longer than patients on daily treatment ($p<0.0001$) and had higher rates of retention on treatment at twelve months (44.2 percent versus 37.1 percent). Dosing frequency was the strongest predictor of time to discontinuation ($p<0.0001$).

Weekly dosing versus monthly dosing

A study compared the relative rates of treatment persistence and medication adherence in patients taking either weekly risedronate or monthly ibandronate.[86] Prescription claims data from the IMS longitudinal prescription database were used to identify patients taking either risedronate 35 mg weekly (n=234,862) or ibandronate 150 mg monthly (n=5,139). Two study periods were

examined: May thru November 2005 and six months after initial market availability of each agent. Prescription refill history was tracked for 180 days from the date the original prescription was filled to evaluate adherence and persistence. Patients being treated with weekly risedronate were found to have significantly higher mean persistence and compliance rates than those patients receiving monthly ibandronate.

Summary

Clinical trials have shown a decreased risk of fractures with alendronate (Fosamax), calcitonin (Fortical, Miacalcin), ibandronate (Boniva), raloxifene (Evista), risedronate (Actonel), and teriparatide (Forteo) in women with osteoporosis. The data are less clear in women who are postmenopausal but have not been diagnosed with osteoporosis. Additionally, data in men show an increase in BMD but a less clear picture on fracture reduction.

Teriparatide (Forteo) showed the greatest increase in BMD in clinical trials, ranging from five to more than 10 percent. In general, the bisphosphonates increased BMD about two to five percent in patients in randomized, controlled trials. Gains in BMD vary by the bone measured, however; BMD gains are greater in vertebral sites compared to those found in hips. Calcitonin (Miacalcin, Fortical) and raloxifene (Evista) show BMD increases of approximately of one to two percent.

Ibandronate (Boniva) and risedronate (Actonel) are both available in a once monthly dosage form. Risedronate (Actonel) is also available in a dosing regimen that is taken two consecutive days each month. Based currently available studies, it appears that bisphosphonates dosed weekly foster greater medication adherence as well as longer treatment persistence compared to daily dosing regimens. However, when compared to once-weekly regimens, once monthly dosing regimens do not appear to give rise to greater treatment adherence and persistence.

Teriparatide (Forteo) should be reserved for patients who have failed other therapies and are also at high risk for fractures. Teriparatide (Forteo) does have a black box warning and also can increase calcium levels.

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