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IBANDRONATE (Boniva™)

A NEW BISPHOSPHONATE FOR THE PREVENTION AND TREATMENT OF OSTEOPOROSIS

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Introduction

Osteoporosis is a disease characterized by deterioration of bone tissue and low bone density that increases the risk of fractures. Observational studies suggest that the risk of fractures increases approximately two-fold for a one standard deviation decrease in bone mineral density (BMD).[1] In the United States alone, 10 million people (8 million women, 2 million men) have osteoporosis and 34 million more are believed to have low bone mass with an increased risk for osteoporosis.[2] Approximately one out of three postmenopausal women =50 years old is affected by osteoporosis.[3] In fact, 50% of women over the age of 50 will suffer an osteoporosis-related fracture during their lifetime.[3] Of the 1.5 million annual fractures, 700,000 are vertebral, 300,000 hip, 250,000 wrist, and 300,000 other.[2] In 2001, the estimated direct cost for osteoporosis-related fractures was $17 billion or roughly $47 million each day.[2]

There are several risk factors that have been associated with development of the disease. Risk factors include but are not limited to advanced age, family history of osteoporosis, or a fracture in a 1st degree relative. Other risk factors include early menopause, a diet low in calcium, having a small frame, being Caucasian or Asian, and certain medications such as long-term systemic corticosteroids. Currently, there are several treatment options for osteoporosis including hormone replacement therapy, raloxifene (Evista®), and calcitonin (Miacalcin®) often in combination with supplemental calcium and vitamin D. Additionally, the bisphosphonates are frequently used for the prevention and treatment of osteoporosis.

Ibandronate (Boniva™) is a new bisphosphonate that was approved by the FDA in May 2003 but is not yet commercially available.[4] Ibandronate 2.5 mg tablets given once-daily is indicated for the treatment and prevention of osteoporosis in postmenopausal women (see Table 1).[6] It will be co-promoted by Roche and GlaxoSmithKline, however, the launch date, commercial dosage form, and cost of the product are still pending. Currently, researchers are trying to find more convenient alternatives to the approved once-daily dosage form.[5] Investigators are studying weekly and monthly oral and parenteral dosage forms, respectively.[11,12] Similar to alendronate (Fosamax®) and risedronate (Actonel®), ibandronate has been shown to decrease the risk of new fractures and increase BMD of the lumbar spine in postmenopausal women.[6,7,8] Of these agents, only alendronate and risedronate have

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Table 1. FDA-approved bisphosphonates[13]

Agent	Dosage Form	Indications
alendronate (Fosamax®)*	Oral	Glucocorticoid-induced osteoporosis Paget's disease osteoporosis in men prevention and treatment of postmenopausal osteoporosis
etidronate disodium (Didronel®)	IV, Oral	Paget's disease heterotopic ossification hypercalcemia of malignancy
ibandronate sodium (Boniva™)	Oral§	Prevention and treatment of postmenopausal osteoporosis
pamidronate (Aredia®)	IV	Hypercalcemia of malignancy Paget's disease osteolytic bone lesions associated with multiple myeloma or metastatic breast cancer
risedronate (Actonel®)*	Oral	Glucocorticoid-induced osteoporosis, Paget's disease, and prevention and treatment of postmenopausal osteoporosis
zoledronate (Zometa®)	IV	Hypercalcemia of malignancy, multiple myeloma, and osteolytic metastases

FDA=Food and Drug Adminstration, IV=intravenous
*Fosamax and Actonel are available in both daily and weekly dosage forms. §Not commercially available in the U.S.

been proven in large randomized clinical trials to decrease the risk of hip fracture.[7,8,9] This article will focus on the pharmacokinetics, safety, and efficacy of ibandronate in women with postmenopausal osteoporosis.

Mechanism of Action

Similar to other bisphosphonates, ibandronate inhibits osteoclast activity thereby reducing bone resorption. Bisphosphonates possess a double phosphate functional group that allows them to bind to calcified bone matrix.[10] When bisphosphonates adsorb to hydroxyapatite in the bone matrix, the matrix becomes less soluble and more stable.[10] Binding of the bisphosphonates to the mineralized hydroxyapatite may inhibit the attachment of osteoclast precursors thereby preventing their transformation into functional osteoclasts.[10]

Pharmacokinetics

The mean oral bioavailability of ibandronate is only 0.6% compared to intravenous (IV) dosing.[6] Also, concomitant administration with foods or beverages other than plain water can impair absorption of the drug by approximately 90%.[6] Ibandronate should be taken at least one hour prior to ingesting any foods or beverages (other than plain water).[6]

Based on two studies, *in vitro* protein binding ranged from approximately 85% to 99%.[6] Approximately 40 to 50% of the absorbed dose is expected to be absorbed into the bone.[6] Ibandronate is not metabolized by the liver and does not inhibit the hepatic cytochrome P450 system, therefore, no dosage adjustment is necessary in patients with hepatic impairment.[6]

Unabsorbed ibandronate is excreted in the feces. Of the portion that is absorbed into the circulation, 50 to 60% is eliminated in the urine as the parent compound.[6] While peak plasma levels are only 10% eight hours after oral dosing, the terminal half-life may be up to 60 hours.[6] Renal clearance of the drug is linearly related to creatinine clearance (CrCl). Therefore, it is not recommended that patients with CrCl <30 mL/min use this drug.[6] No dosage adjustment is necessary in patients with mild to moderate renal impairment (e.g. CrCl =30 mL/min) or in the elderly.[6]

Clinical Studies

Treatment of Postmenopausal Osteoporosis

In a randomized, double-blind, placebo-controlled, parallel group study, 2946 postmeno-

Table 2. Incidence of new vertebral fractures in 3-year treatment study[6]

Type of Fracture	Placebo (N=975)	Ibandronate (N=977)	ARR (95% CI)	RRR (95% CI)
New Vertebral Fracture	9.6	4.7	4.9 (2.3, 7.4)	52 (29,68)
New and Worsening Vertebral Fracture	10.4	5.1	5.3 (2.6, 7.9)	52 (30, 67)
Clinical (Symptomatic) Vertebral Fracture	5.3	2.8	2.5 (0.6, 4.5)	49 (14, 69)

N= number of patients, QD= once daily, ARR=absolute risk reduction, CI=confidence interval, RRR=relative risk reduction
* Data based on an intent-to-treat analysis with the last measured value carried forward.

pausal women with osteoporosis aged 55 to 80 years were given either ibandronate 2.5 mg daily, 20 mg intermittently, or placebo.[6] Women who had a lumbar spine BMD T-score two to five standard deviations below the pre-menopausal mean in at least one vertebra (L1-L4), and who had one to four prevalent fractures were included in the study.[6] The primary endpoint of the study was new vertebral fractures after 3 years of treatment. All of the women in the study received concomitant calcium 500 mg and vitamin D 400 IU each day. After 3 years, the patients taking ibandronate 2.5 mg daily (n=977) had a 4.9% absolute risk reduction for new vertebral fractures compared to placebo (n=975) ($p<0.001$) (see Table 2). There were no differences among the groups with respect to the number of fractures reported in the pelvis, femur, wrist, forearm, rib, or hip. While not identified as primary endpoints, patients in the ibandronate 2.5 mg daily treatment arm demonstrated a 6.4%, 3.1%, 2.6%, and 5.3% mean increase from baseline in BMD of the lumbar spine, total hip, femoral neck, and trochanter, respectively (see Table 3).

Table 3. Mean % change in BMD from baseline in 3-year treatment study[6]

Site	Placebo	Ibandronate
Lumbar Spine	1.4 (N=693)	6.4 (N=714)
Total Hip	-0.7 (N=638)	3.1 (N=654)
Femoral Neck	-0.7 (N=683)	2.6 (N=699)
Trochanter	0.2 (N=683)	5.3 (N=699)

BMD=bone mineral density
* Data based on an intent-to-treat analysis with the last measured value carried forward.

Prevention of Postmenopausal Osteoporosis

In a randomized, double-blind, placebo-controlled study, 653 postmenopausal women without osteoporosis (lumbar spine BMD T-scores >-2.5) aged 41 to 82 years were given either ibandronate 0.5 mg, 1.0 mg, 2.5 mg, or placebo in addition to 500 mg of supplemental calcium daily.[6] Patients were stratified according to baseline lumbar spine BMD and time since menopause. The primary endpoint of the study was the change in BMD of the lumbar spine after 2 years of treatment. Patients given ibandronate 2.5 mg daily had a mean increase in lumbar spine BMD of 3.1% compared to placebo ($p<0.001$). Although not the primary endpoint, patients randomized to ibandronate 2.5 mg demonstrated a mean increase in BMD of 1.8%, 2.0%, and 2.1% of the total hip, femoral neck, and trochanter, respectively.

Adverse Events

The percentage of patients who withdrew from the studies described above due to adverse events was 17% in both the active and placebo arms with the most common reason being related to the digestive tract.[6] According to the prescribing information, the incidence of adverse events appeared to be similar between the ibandronate 2.5 mg daily and placebo groups. The most common adverse effects experienced in the placebo and ibandronate groups respectively included: upper respiratory infection (33.2%, 33.7%), back pain (12.2%, 13.5%), dyspepsia (9.8%, 11.9%), and bronchitis (6.8%, 10.0%) (see Table 4).[6]

Dosage and Administration

Ibandronate should be administered on an empty stomach at least 60 minutes prior to eating or drinking anything other than plain water.[6] The 2.5

Table 4. Adverse events occurring in >5% of patients[6]

Adverse Event	Placebo (N=1134)	Ibandronate (N=1140)
Upper respiratory infection	33.2	33.7
Back pain	12.2	13.5
Dyspepsia	9.8	11.9
Bronchitis	6.8	10.0
Pain in extremity	6.4	7.8
Diarrhea	5.0	6.8
Headache	5.8	6.5
Pneumonia	4.3	5.9
Myalgia	5.1	5.7

* Table adapted from CDER approved labeling for ibandronate.

mg tablets, if marketed, should be swallowed whole with 8 ounces of plain water, and the patient should avoid lying down for at least one hour after taking the drug. Recommend that women with postmenopausal osteoporosis obtain up to 1500 mg of calcium and 400 IU of Vitamin D daily either from their diet or from dietary supplements.[2,14]

Summary

Bisphosphonates play a central role in the prevention and treatment of osteoporosis. Use of ibandronate in postmenopausal women reduced the risk of new vertebral fractures and demonstrated increased mean lumbar BMD compared to placebo. The adverse event profile of the drug appeared to be similar to placebo in these controlled clinical studies. The methodologies and statistical analyses of the studies summarized above were not evaluated because they have not been published in the primary literature.

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New Formulations

Prempro® In addition to the recently approved 0.45mg/1.5mg dose of conjugated estrogens/MPA, Wyeth has received approval for a 0.3mg/1.5mg dose. Both agents are approved for the treatment of moderate to severe vasomotor symptoms associated with menopause and for the prevention of postmenopausal osteoporosis. The 0.45mg dose should be available this summer, while the 0.3mg product is expected to be available by the end of the year.

Avonex® Biogen will soon have available new prefilled syringes that will make their once-a-week treatment for multiple sclerosis more convenient to administer.

Teriparatide (Forteo®)

Promising treatment for patients at increased risk for osteoporosis-related fractures

Patria Rorie, Pharm.D. Candidate

Introduction

Osteoporosis is prevalent worldwide, and its occurrence is projected to increase as life expectancy increases and the population ages. It is estimated that 18 million Americans have low hip bone density, with an additional 10 million having osteoporosis of the hip. Approximately 1.5 million osteoporotic fractures occur annually in the United States.[1]

It may be difficult to differentiate between osteoporosis and bone abnormalities associated with aging, however evidence supports that low bone density increases in both men and women as they age. Osteoporosis is more common among women than men due to the following factors: 1) women live longer than men; 2) most healthy men, before the age of 50, have approximately 33% more bone mass than women: 3) men have the tendency to be more active physically than women of the same age; and 4) osteoporosis progresses more rapidly in postmenopausal women, especially within 5 years after menopause, due to the sudden decline in hormonal production vs. men who experience a gradual reduction in testosterone levels with age.

Immediately after menopause, there is about 5 to 10 times more bone loss in women compared to men of the same age. It appears that whites have lower bone mass than blacks. The incidence of hip fractures and complications associated with osteoporosis among white women 65 years of age and older is higher than strokes, breast cancer, and diabetes. By the age of 70, approximately 40% of women experience at least one fracture; by the age of 90, more than 33% of women and 17% of men will have suffered a bone fracture and, between 12% and 20% of this group die of complications of osteoporosis, particularly hip fractures. The economic burden caused by osteoporosis is high. The annual costs of fractures associated with this disease in the USA range from $10 to $15 billion.

Teriparatide, manufactured by Eli Lily, was approved by the Food and Drug Administration (FDA) in November 2002 for the treatment of osteoporosis in postmenopausal women who are at high risk for having a fracture. The drug is also approved to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fractures.[2] This article will examine the pharmacology, pharmacokinetics, clinical trial data, safety, cost, and dosing considerations of teriparatide.

Pharmacology and Pharmacokinetics

Forteo® [teriparatide (rDNA origin) injection] contains recombinant human parathyroid hormone (1-34), [rhPTH(1-34)], which has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. Studies have shown that PTH promotes new bone formation by preferentially stimulating osteoblastic activity over osteoclastic activity, a fundamentally different mechanism than seen in antiresorptive agents (i.e. estrogen and bisphosphonates) already in use, which merely prevent further bone loss.[3]

Teriparatide is administered as a subcutaneous injection with an absolute bioavailability reaching approximately 95%. The rates of absorption and elimination of the drug are rapid; a 20-mcg dose results in peak serum concentrations approximately 30 minutes after administration and concentrations decline to non-quantifiable levels within 3 hours. Systemic clearance (approximately 62 L/hr in women and 94 L/hr in men) of teriparatide exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance.

Volume of distribution following intravenous injection is approximately 0.12 L/kg. Intersubject variability in systemic clearance and volume of distribution is 25—50%. The half-life of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection. The longer half-life following subcutaneous administration reflects delayed absorption from the

Table 1. Effects of teriparatide on risk for new nonvertebral fractures in postmenopausal women with osteoporosis[5]

Fracture Site	Teriparatide† (N=541)	Placebo† (N=544)
Wrist	2 (0.4%)	7 (1.3%)
Ribs	3 (0.6%)	5 (0.9%)
Hip	1 (0.2%)	4 (0.7%)
Ankle/Foot	1 (0.2%)	4 (0.7%)
Humerus	2 (0.4%)	2 (0.4%)
Pelvis	0 (0.0%)	3 (0.6%)
Other	6 (1.1%)	8 (1.5%)
Total (%)	14 (2.6%)*	30 (5.5%)

*p< 0.05 compared with placebo, † data shown as number (%) of women with fractures

injection site. Peripheral metabolism of intact PTH, the 34 N-terminal amino acids, and, presumably, teriparatide, is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys.

The pharmacokinetic parameters of teriparatide appear to be similar across an age range of 31—85 years. The systemic exposure of teriparatide is 20—30% lower in men compared to women, although the recommended dose for both genders is 20 mcg/day. Teriparatide, as a single dose, has no pharmacokinetic differences in a limited number of patients with mild to moderate renal insufficiency (i.e., CrCl 30—72 ml/min) compared to healthy controls. In patients with severe renal insufficiency (i.e., CrCl <30 ml/min), the area under the curve (AUC) and half-life were increased by 73% and 77% respectively; however, maximum serum concentrations of teriparatide were not increased.

No information is available for patients undergoing dialysis. The pharmacokinetic parameters of teriparatide appear to be similar in patients with NYHA Class I—III heart failure, and no clinically relevant changes in blood pressure or pulse rate were noted. Teriparatide has not been studied in patients with hepatic impairment.[4]

Clinical Trials

The FDA's approval of teriparatide was based on 24 clinical trials enrolling more than 2,800 postmenopausal women and men with osteoporosis. Phase III clinical trial data showed that teriparatide stimulated new bone formation, lowered the risk of vertebral (spinal) fractures and increased bone mineral density (BMD) compared with placebo in postmenopausal women with osteoporosis during an average of 19 months of treatment. The data also showed that teriparatide reduced the relative risk of spinal fractures by 65 percent (9.3% absolute risk reduction) and lowered the overall relative risk of non-spinal fractures (wrist, ribs, hip, ankle/foot, etc.) by 53% (2.6% absolute risk reduction) when compared to placebo (Table 1).

Teriparatide also significantly increased spine BMD in postmenopausal women with osteoporosis beginning at three months of treatment. The data showed that 96% of women had an increase in BMD from baseline, with 72 percent achieving at least a 5% increase in spine BMD and 44 percent gaining 10% or more compared to placebo. The increases in BMD seen in patients treated with teriparatide were statistically significant ($p<0.001$).[4]

Postmenopausal Women with Osteoporosis

The largest clinical study with teriparatide was the Fracture Prevention Trial. This trial was a double-blind, randomized, placebo-controlled multinational trial in 1637 women with osteoporosis and prior vertebral fractures. Subjects received teriparatide 20 mcg, 40 mcg, or placebo as a once daily subcutaneous injection for a median duration of 19 months. Teriparatide reduced the incidence of 1 or more vertebral fractures from 14.3% of women in the placebo group to 5.0% in the teriparatide group. This difference was found to be statistically significant ($p<0.001$).[5]

Table 2. Summary of adverse events occurring in > 1% of placebo and teriparatide-treated patients[4]

Adverse Event	Placebo	Teriparatide 20 mcg	*p*-value
Back Pain	22.6%	16.8%	0.017
Nausea	7.5%	9.4%	0.264
Headache	8.3%	8.1%	0.934
Leg Cramps	1.1%	3.1%	0.020
Cyst	0.9%	1.7%	0.277
Syncope	1.7%	3.1%	0.109
Nail Disorder	0.4%	1.3%	0.093

Men

The efficacy and safety of teriparatide were investigated in a double-blind, randomized, placebo-controlled multinational trial that involved 437 men with hypogonadal or primary osteoporosis and a BMD of the spine or hip of > 2 SD below the mean. Subjects received teriparatide 20 mcg, 40 mcg, or placebo as a once daily subcutaneous injection for a median duration of 11 months. The primary study endpoint was the number of subjects experiencing a change in lumbar spine BMD. Teriparatide significantly increased lumbar spine BMD (5.9%) compared to the placebo group (0.5%); ($p<0.001$).[4]

Comparison to Alendronate

A randomized double-blind clinical trial enrolled 146 postmenopausal women with osteoporosis to compare the efficacy of teriparatide 40 mcg to alendronate 10 mg. Median duration of exposure was 14 months. The primary endpoint of the study was the change in lumbar spine BMD, which showed an increase of 12.2% in the teriparatide group compared to a 5.6% increase in the alendronate group ($p<0.001$).[4]

Dosing and Administration

Teriparatide is administered by injection once a day in the thigh or abdomen. The recommended dose is 20 mcg per day. Teriparatide should initially be administered under circumstances where the patient can sit or lie down in case symptoms of orthostatic hypotension occur. Visually inspect teriparatide injection solution for particulate matter and discoloration prior to administration. Do not use injection solutions that are cloudy or colored. Each Forteo™ Pen can be used for up to 28 days after the first injection. After a 28-day use period, the pen should be discarded, even if it still contains unused solution. The Forteo™ Pen administration device should not be shared. Persons with hyperkalemia, women who are pregnant or nursing, or persons who have ever been diagnosed with bone cancer or other cancers that have spread to the bones, should not use teriparatide. Because the effects of long-term treatment with teriparatide are not known at this time, therapy for more than 2 years is not recommended.[6]

Toxicity and Safety

In animal studies with teriparatide, there was an increase in the number of rats developing osteosarcoma, a rare but serious cancer of the bone. In the human studies, no osteosarcomas were reported, but the possibility that humans treated with teriparatide may face an increased risk of developing this cancer cannot be ruled out. This safety issue is highlighted in a black box warning in the drug's label for health professionals and explained in a brochure, called a Medication Guide, for patients. To help ensure that patients are aware of important information about teriparatide, the Medication Guide will be distributed by the pharmacist each time the drug is dispensed. Because people with growing bones and people with Paget's disease of the bone have a higher risk for developing osteosarcoma, it is important that they not be treated with teriparatide.

Teriparatide has not been studied in pediatric populations and should not be used in pediatric patients or young adults with open epiphyses. Most side effects reported in association with teriparatide in clinical trials were mild and included nausea, dizziness, and leg cramps (Table 2). During the

Table 3. Cost Comparison of Forteo® 20 mcg/day

Pharmacy	Price
Retail (chain)	$567.95
Independent	$583.00
Internet	$515.96
Mean Price	$555.64

clinical trials, early discontinuation due to adverse events occurred in 5.6% of patients assigned to placebo and 7.1% of patients taking teriparatide.

Cost

The retail cost for a 30-day supply is summarized in Table 3.

Summary

Teriparatide is the first treatment for osteoporosis that has been proven to promote new bone formation and has been proven effective in clinical trials for both women and men who are at risk of osteoporosis-related fractures. Although it is generally well-tolerated, some safety concerns remain and the drug is labeled with a black box warning, indicating the need for additional safety studies. It appears to be an effective treatment option for patients at risk for fractures from advanced osteoporosis.

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Fuzeon™ (enfuvirtide) is the first of a new class of drugs called fusion inhibitors. It is also the first class of drugs developed and approved for the treatment of HIV since 1996. It should be used in combination with other antiretroviral agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. The usual dose is 90 mg SQ twice a day.

Velcade™ (bortezomib) is the first in a new class of antineoplastic agents known as proteosome inhibitors. Inhibition of this enzyme complex has demonstrated to disrupt cell homeostasis and in vitro, has lead to death of a variety of cancer cell types. It has been approved for the treatment of multiple myeloma in patients who have demonstrated disease progression despite receiving at least two prior therapies. The initial dosage is 1.3 mg/m^2/dose IV bolus twice weekly for 2 weeks followed by a 10-day rest period.

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