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BONIVA®: A NEW OPTION FOR THE PREVENTION AND TREATMENT OF OSTEOPOROSIS

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Osteoporosis is a global health concern that results in significant morbidity and mortality and increased healthcare costs. In the United States (US) alone, it is estimated that 1.5 million people experience osteoporotic related fractures with associated costs of \$14 billion each year.^{1,2} Of these fractures, estimates indicate 700,000 vertebral fractures, 250,000 hip fractures, 250,000 wrist fractures, and 300,000 other limb fractures.³ Morbidity associated with fractures can greatly interfere with activities of daily living (ADL). After a vertebral fracture, 80-90% of patients experience chronic pain and 70% have difficulty completing ADL.⁴ One year after a hip fracture, up to 40% of women are unable to walk independently and 60-80% are unable to perform basic ADL.⁵ In spite of the large number of affected individuals, 80% who have experienced at least one fracture, are neither identified or treated.^{1,6} This is a testament to the fact that there is a need to implement aggressive therapy for the prevention and treatment of osteoporosis.

Osteoporosis results from an uncoupling of osteoclastic and osteoblastic activity, with bone loss occurring as a result of excess bone resorption.⁷ Osteoporosis is "characterized by low bone mass and microarchitectural deterioration of bone

tissue leading to enhanced bone fragility and a consequent increase in fracture risk."⁸ It can be clinically categorized as: postmenopausal osteoporosis (PMO), characterized mainly by vertebral and distal forearm fractures; age-related osteoporosis, beginning shortly after peak bone mass is obtained and affecting both cortical and trabecular bone; or secondary osteoporosis, caused by medications or diseases affecting both types of bone.⁷

Fractures represent the major complications associated with osteoporosis. Since low bone mineral density (BMD) is a major risk factor for fractures, treatment for osteoporosis aims to prevent bone loss or increase BMD in hopes of reducing the risk of fractures.⁹ The World Health Organization (WHO) classifies BMD based on *t-scores*, a comparison of the patient's BMD with a reference population at peak BMD.¹⁰ (Table 1) In the US, it is estimated that 54% of white postmenopausal women are osteopenic and 30% are osteoporotic, and that by age 80, 27% of women are osteopenic and 70% are osteoporotic.¹¹ Furthermore, in any 10 year period white postmenopausal women will experience 5.2 million fractures of the hip, spine or distal forearm, resulting in over \$45 billion in direct medical expenditures.¹² The decision to treat warrants careful consideration of available therapeutic options and an assessment of the patient's risk for fracture.⁹ Criteria have been estab-

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Table 1. WHO definition of Osteoporosis.¹⁰

<i>t-score</i> [†]	Classification
Above -1.0	Normal
-1.0 to -2.5	Osteopenia or low BMD
Below -2.5	Osteoporosis
Below -2.5 plus fractures	Severe osteoporosis

[†] *t-score* is the patients BMD compared with the mean BMD of a reference population at peak BMD (age 25 years). Data adapted from [10]

lished that endorse initiating treatment in the following patient groups: *t-score* below -1.5 plus additional risk factors for fracture, *t-score* below -2.0, and age above 70 years plus additional risk factors.⁸

Currently available therapies for the prevention and treatment of PMO include: calcium and vitamin D, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMS) and other estrogen analogues, bisphosphonates, calcitonin, and parathyroid hormone (PTH).⁹ The use of calcium and vitamin D is insufficient for the treatment of osteoporosis, but must accompany all pharmacologic therapies. Although there are no current recommendations as to which class of agents should be the first-line choice, bisphosphonates have emerged as an important treatment option. There are currently three FDA-approved bisphosphonates for the prevention and treatment of PMO.¹⁴ (Table 2)

The management of osteoporosis requires lifelong adherence to interventions to reduce the risk of fractures. It is important that adequate intake of calcium and vitamin D be maintained by patients receiving bisphosphonate therapy. The National Osteoporosis Foundation (NOF) suggests a daily dietary calcium intake of at least 1200 mg and vitamin D 400-800 IU/day for individuals at risk.¹³ Alendronate and risedronate have been shown to reduce vertebral and non-vertebral fracture risk and have been associated with increased BMD.¹⁴ In addition to the once-daily formulations, both are available in a once-weekly formulation. Analyses of prescription data suggests that adherence is better to once-weekly dosing regimens when compared to once-daily, however the overall persistence and adherence to therapy at one year still remains suboptimal, perhaps due to the cumbersome dosing requirements with this class of drugs.^{15,16}

Roche Pharmaceuticals in conjunction with GlaxoSmithKline announced on March 25, 2005 the approval of their supplemental new drug application

(sNDA) for ibandronate (Boniva[®]) 150 mg tablets. Ibandronate 150 mg is the first and only once-monthly oral medication for the treatment and prevention of PMO.¹⁷ Although ibandronate was previously approved as a once-daily dosage regimen, it was never marketed in the US. The new once-monthly dosage form was made available by prescription in US pharmacies in April 2005. Once-monthly ibandronate provides patients with another option for osteoporosis prevention and treatment that may increase adherence. This article will examine the role of once-monthly ibandronate for the prevention and treatment of postmenopausal osteoporosis.

Pharmacology and Pharmacokinetics

Ibandronate's mechanism of action (MOA) is in part mediated by its binding to hydroxyapatite which is part of the mineral matrix of bone. Ibandronate's chemical structure confers enhanced binding to hydroxyapatite and increased affinity for calcium in bone.¹⁴ The antiresorptive effects of ibandronate result from actions on osteoclast activity including: inhibition of osteoclast recruitment and activity on the bone surface, induction of osteoclast apoptosis, and alterations in bone mineral that reduce the rate of dissolution.^{14,18} Ibandronate produces measurable biochemical changes indicative of decreased bone resorption, such as decreases in deoxypyridinoline and cross-linked C-telopeptide of Type I collagen.¹⁸

Ibandronate's mean peak plasma concentration is achieved within 0.5 to 2.0 hours after oral administration when fasting. Absorption takes place in the upper gastrointestinal (GI) tract and is impaired by food or beverages other than water. Oral bioavailability of ibandronate 2.5 mg is approximately 0.6% compared to intravenous dosing, and is reduced by as much as 90% when it is taken with a meal. Following absorption, ibandronate is rapidly bound to bone or excreted in the urine. Ibandronate has a volume of distribution (V_d) of at least 90 L with 40% to 50% of the circulating dose binding to bone. There is no evidence that ibandronate is metabolized, and the portion not removed from circulation by bone uptake is eliminated unchanged by the kidneys. Ibandronate not absorbed by the gut is eliminated unchanged in the feces. Ibandronate exhibits multiphasic elimination, with a slower clearance phase as it redistributes back into circulation from bone. The observed terminal half-life in healthy post-menopausal women who received ibandronate 150 mg varied between 37 to

Table 2. FDA approved bisphosphonates for the treatment of postmenopausal osteoporosis.¹⁴

Drug Name	Once-daily dose	Once-weekly dose	Once-monthly dose
Alendronate (Fosamax [®])	10 mg every day	70 mg every week	
Risedronate (Actonel [®])	5 mg every day	35 mg every week	
Ibandronate (Boniva [®])	2.5 mg every day [†]		150 mg every month [‡]

[†]Not marketed in the US, [‡]Approved on March 24, 2005.

157 hours, and was found to be dependent on the dose and assay sensitivity. Ibandronate exerts favorable effects on bone turnover months to years following discontinuation of therapy due to its high affinity for hydroxyapatite and slow redistribution from bone to plasma.¹⁸

Due to its exclusive renal elimination, the clearance of ibandronate is decreased with impaired renal function. In patients given ibandronate 0.5 mg intravenously, those with a creatinine clearance (CrCL) of 40 to 70 mL/min had a 55% higher area under the curve (AUC) than those patients with a CrCL >90 mL/min. Patients with a CrCL <30 mL/min had more than a two-fold increase in exposure. No gender differences were identified in bioavailability and pharmacokinetics of ibandronate, and any pharmacokinetic differences due to race have not been studied.¹⁸

Clinical Trials

Treatment of Postmenopausal Osteoporosis

The oral ibandronate osteoporosis vertebral fracture trial in North America and Europe (BONE) was a 3-year, multinational, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of ibandronate for the treatment of PMO in 2946 women.¹⁹ Patients were randomized to receive ibandronate 2.5 mg every day, ibandronate 20 mg intermittently (20 mg every other day x 12 doses every 3 months), or placebo. All patients received 400 IU vitamin D and 500 mg calcium at bedtime. Patient baseline demographic characteristics were comparable among the three treatment groups. Inclusion criteria were: 55-80 years of age, at least 5 years post-menopausal, lumbar spine BMD *t*-scores between -2.0 and -5.0 in at least one vertebra (L1-L4), and 1 to 4 baseline vertebral fractures. The primary endpoint measured in this intention-to-treat trial was the incidence of new vertebral fractures. The secondary endpoints included: incidence of new

or worsening vertebral fractures, clinical vertebral fractures, clinical osteoporotic nonvertebral fractures, relative change in BMD and bone turnover markers, and change in height.^{18,19}

At 3 years, both ibandronate treatment groups produced statistically significant decreases in the incidence of new vertebral fractures and new or worsening vertebral fractures compared with placebo. (Table 3) There was no difference in the antifracture efficacy between the two ibandronate treatment groups. No statistically significant difference was observed in the incidence of nonvertebral fractures across the three treatment groups (Table 3). However, a post-hoc analysis of patients at higher risk for nonvertebral fractures (defined as a baseline femoral neck BMD *t*-score < -3.0) revealed that treatment with ibandronate 2.5 mg every day resulted in a statistically significant reduction in the incidence of nonvertebral fractures (relative risk reduction [RRR] 69%, *p*=0.01) at 3 years. The intermittent ibandronate treatment group did not achieve a statistically significant reduction in nonvertebral fractures (RRR 37%, *p*=0.22). Patients in both ibandronate treatment groups had statistically significant increases in BMD at the lumbar spine and hip relative to baseline and compared to placebo. The increase in BMD was statistically significant by 6 months, and was progressive over the 3-year treatment period. The treatment groups also demonstrated statistically significant reductions in markers of bone turnover and height loss compared with the placebo group. The newly formed bone during treatment was found to have normal composition and quality, with no indication of osteomalacia or mineralization defects. Treatment with ibandronate was well tolerated and demonstrated a broad margin of safety with an adverse event profile similar to that of placebo.¹⁹

The monthly oral ibandronate in ladies study (MOBILE) is a 2-year, multinational, randomized, double-blind, non-inferiority study undertaken with

Table 3. Incidence of fractures reported in the BONE Trial.¹⁹

	Placebo (n=975)	Ibandronate 2.5 mg daily [RRR] (n=977)	Ibandronate 20 mg (intermittent)* [RRR] (n=977)
1 st new vertebral fracture	9.6%	4.7% [52%] [†]	4.9% [50%] [†]
1 st new or worsening fracture	10.4%	5.1% [52%]	5.8% [46%]
Clinical vertebral fracture	5.3%	2.8% [49%] [‡]	2.8% [48%] [‡]
Clinical fractures	13.0%	11.6%	11.2%
Nonvertebral fractures	8.2%	9.1%	8.9%

RRR= Relative risk reduction versus placebo. *Intermittent dosing= 20 mg every other day x 12 doses every 3 months. [†]Statistical significance p<0.0005, [‡]Statistical significance p<0.015. Data adapted from reference 19.

the purpose of comparing the safety and efficacy of monthly versus daily ibandronate dosing in the treatment of PMO. The study is currently in its second year, but one-year data for primary and secondary endpoints has been published.²⁰ The 1609 women enrolled met the following criteria: 55-80 years of age, 5 or more years postmenopausal, and a lumbar spine *t-score* between -2.5 and -5.0. The patients were randomized to receive: 50/50 mg monthly (50 mg doses on 2 consecutive days), 100 mg every month, 150 mg every month, or 2.5 mg every day. Since the antifracture efficacy and safety of ibandronate 2.5 mg every day was previously established, this dosing schedule was used as the reference arm.¹⁹ All patients received 400 IU vitamin D and 500 mg calcium. Patient baseline demographic characteristics were comparable across all treatment arms. The primary endpoint is the relative change from baseline in lumbar spine BMD [L2-L4]. Secondary endpoints include the relative change in BMD of the total hip, femoral neck, and trochanter, as well as changes in serum C-telopeptide (sCTX) and a retrospective analysis of bone-specific alkaline phosphatase (BSAP).²⁰

The 1-year analysis demonstrated that monthly ibandronate produced increases in lumbar spine BMD of at least equal magnitude to that produced by ibandronate daily (**Table 4**). Tests for superiority found ibandronate 150 mg once-monthly to be superior to the once-daily regimen with regard to the primary endpoint (p=0.002). The ibandronate monthly regimen was comparable to the once-daily regimen for increases in BMD at all hip sites. The once-monthly ibandronate regimens produced decreases in markers of bone turnover sCTX and BSAP. A responder analysis was done to determine if patients were achieving increases in BMD

that correlate with antifracture efficacy (BMD increases >6% at lumbar spine, or >3% at hip). This analysis showed that when compared to the once-daily regimen, significantly more patients receiving ibandronate 100 mg or 150 mg monthly achieved the aforementioned increases in BMD. Furthermore, a safety analysis showed that monthly ibandronate is well tolerated and has a safety profile similar to that of daily ibandronate.²⁰

Prevention of Postmenopausal Osteoporosis

A randomized, double-blind, placebo-controlled 2-year study of 654 postmenopausal women without osteoporosis at baseline, demonstrated the efficacy of ibandronate 2.5 mg every day for the prevention of bone loss. Inclusion criteria were: women aged 41 to 82 years, average of 8.5 years postmenopausal, lumbar spine BMD *t-scores* > -2.5. Patients were stratified according to years after menopause (1 to 3 years, >3 years) and baseline lumbar spine BMD (*t-scores*: >-1, -1 to -2.5). The study compared ibandronate 0.5 mg, 1.0 mg, or 2.5 mg every day with placebo. All patients received 500 mg of calcium once daily. The primary efficacy measure was a change in lumbar spine BMD at the end of study period. Ibandronate 2.5 mg every day resulted in a mean increase in lumbar spine BMD of 3.1% over placebo. Lumbar spine BMD increases were seen at 6 months and at all later time points when comparing ibandronate 2.5 mg every day to placebo across all four baseline strata. Currently the safety and efficacy of ibandronate 150 mg monthly for the prevention of PMO is being studied.¹⁸

Dosing and Administration

The ibandronate once-monthly formulation is available as a 150 mg film-coated tablet. Ibandronate

Table 4. Mean change from baseline in lumbar spine BMD in the MOBILE Trial.²⁰

	2.5 mg/d (n=318)	50/50 mg/mo. (n=330)	100 mg/mo. (n=315)	150 mg/mo. (n=327)
Change vs. Baseline (%)	3.9	4.3	4.1	4.9 [†]

[†]p=0.002 for comparison versus 2.5 mg/daily.

150 mg tablets should be taken on the same day of each month (i.e., January 15, February 15, etc.). If a patient misses a dose it should be taken on the morning following the date it is remembered. The patient should then continue taking ibandronate according to their original schedule. A patient should not take two 150 mg tablets within the same week. If the missed dose is remembered 1 to 7 days before the next scheduled dose, the patient should skip the missed dose and take the next scheduled dose continuing on their original schedule.¹⁸

Ibandronate should be taken in the morning, at least 60 minutes before the first food or drink (other than water) of the day, and before taking any oral medications containing multivalent cations. To reduce the risk of esophageal irritation, tablets should be swallowed whole with a full glass of plain water while the patient is standing or sitting. The patient should then remain upright for 60 minutes after taking ibandronate.¹⁸

Drug interactions have been identified with products containing calcium and other multivalent cations since they are likely to interfere with the absorption of ibandronate. Like other bisphosphonates, ibandronate does not interfere with cytochrome P450 (CYP450) activity and does not influence the elimination of drugs dependent upon this route of elimination. No drug interaction or increased incidence of adverse effects was reported in patients treated with concomitant aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).¹⁸ However, on the basis of potential additive gastrointestinal mucosal toxicity and post marketing reports with other bisphosphonates, caution is warranted when these agents are used together.¹⁸

Toxicity and Safety

Results from clinical trials comparing treatment with daily ibandronate versus placebo, demonstrated an overall adverse event profile similar to that of placebo.^{18,19} Results from the MOBILE study found that ibandronate 150 mg monthly was gener-

Table 5. Monthly retail cost of bisphosphonate therapy.

Drug	Cost (\$/month)
Alendronate (Fosamax[®])	\$ 76.90
Ibandronate (Boniva[®])[†]	\$ 80.37
Risedronate (Actonel[®])	\$ 75.95

Average retail cost from 3 community pharmacies in Gainesville, FL 32601.

ally well-tolerated and has a safety profile similar to that of daily ibandronate.²⁰ The most commonly reported adverse events included hypertension, dyspepsia, arthralgia, back pain, nausea, and diarrhea. Upper GI events were rare in the four treatment arms of the MOBILE study and no differences were observed among treatment groups. The most common complaints were dyspepsia, nausea, and abdominal pain. Overall, the incidence of GI adverse events was higher in patients taking NSAIDs and those with a history of GI disorders, however there were no differences in the incidence of adverse events across the four treatment arms. The incidence of influenza-like illness was higher in the monthly treatment groups (6.6%-8.3%) compared with the daily group (2.8%). However, the majority of adverse events occurring after the first dose, were short in duration, and resolved without treatment.²⁰

Contraindications to the use of ibandronate include: known hypersensitivity to ibandronate or to any of its excipients, uncorrected hypocalcemia, or an inability to stand or sit upright for at least 60 minutes. Ibandronate is not recommended for use by patients with severe renal impairment defined as a CrCL <30 mL/min.¹⁸

Cost

As of April 2005, Boniva[®] was made available by prescription in US pharmacies. It comes packaged as a 3-month supply (3 tablets). **Table 5** lists the average retail cost for Boniva[®] compared to the cost of the other bisphosphonates.

Summary

Ibandronate (Boniva[®]) 150 mg is the first once-monthly oral medication for the treatment of any chronic disease. Ibandronate is indicated for the prevention and treatment of postmenopausal osteoporosis. Ibandronate is effective in treating postmenopausal osteoporosis by increasing bone mass density and decreasing the risk of vertebral

fractures. Newly formed bone is of normal quality and has no indication of osteomalacia or mineralization defects. Ibandronate decreases nonvertebral fractures in a subgroup of postmenopausal women at higher risk for fractures (femoral neck *t-scores* < -3.0).

The main benefit of ibandronate over other available bisphosphonates may be the more convenient dosing regimen. As a once-monthly drug, ibandronate is an alternative for patients struggling with the administration of bisphosphonates either daily or weekly. The once-monthly regimen may help increase adherence to drug therapy. Further studies are needed to determine the full benefits of ibandronate on nonvertebral fractures. Head-to-head trials with available bisphosphonates are warranted to better establish the role of ibandronate for postmenopausal osteoporosis.

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New Drug Approvals

Ramelteon (Rozerem[™], Takeda Pharmaceuticals), the first melatonin receptor agonist, is approved for the treatment of acute or chronic insomnia. Unique among agents used to treat insomnia, Rozerem[™] is not a controlled substance. The approved dose is one 8 mg tablet 30 minutes before bedtime. It should not be prescribed to patients with severe hepatic impairment or those receiving fluvoxamine.

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