CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

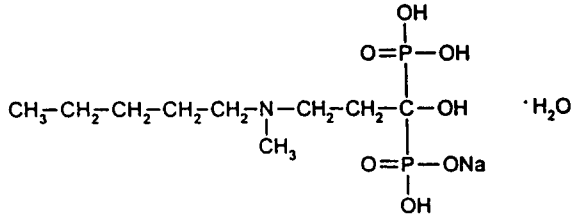
21-455

APPROVED LABELING

BONIVA™
(ibandronate sodium)
TABLETS

DESCRIPTION

BONIVA (ibandronate sodium) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The chemical name for ibandronate sodium is 3-(*N*-methyl-*N*-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula $C_9H_{22}NO_7P_2Na \cdot H_2O$ and a molecular weight of 359.24. Ibandronate sodium is a white to off-white powder. It is freely soluble in water and practically insoluble in organic solvents. Ibandronate sodium has the following structural formula:



BONIVA is available as a white, oblong, 2.5-mg film-coated tablet for oral administration. One tablet contains 2.813 mg ibandronate monosodium monohydrate, equivalent to 2.5 mg free acid. BONIVA also contains the following inactive ingredients: lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000, and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action

The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

Pharmacokinetics

Absorption

The absorption of ibandronate occurs in the upper gastrointestinal tract. After a 2.5 mg oral dose, the time to maximum observed plasma ibandronate concentrations ranged from 0.5 to 2 hours (median 1 hour) in fasted healthy postmenopausal women. The mean oral bioavailability of 2.5 mg ibandronate was about 0.6% compared to intravenous dosing. The extent of absorption is impaired by food or beverages (other than plain water). The oral bioavailability of ibandronate is reduced by about 90% when BONIVA is administered with a standard breakfast in comparison with bioavailability observed in fasted subjects. There is no meaningful reduction in bioavailability when ibandronate is taken at least 60 minutes before a meal.

However, both bioavailability and the effect on bone mineral density (BMD) are reduced when food or beverages are taken less than 60 minutes following an ibandronate dose.

Distribution

After absorption, ibandronate either rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 L, and the amount of dose removed from the circulation via the bone is estimated to be 40% to 50% of the circulating dose. In vitro protein binding in human serum was 99.5% to 90.9% over an ibandronate concentration range of 2 to 10 ng/mL in one study and approximately 85.7% over a concentration range of 0.5 to 10 ng/mL in another study.

Metabolism

There is no evidence that ibandronate is metabolized in humans.

Elimination

The portion of ibandronate that is not removed from the circulation via bone absorption is eliminated unchanged by the kidney (approximately 50% to 60% of the absorbed dose). Unabsorbed ibandronate is eliminated unchanged in the feces.

The range of observed apparent half-lives is broad and dependent on the dose studied and on assay sensitivity, but the apparent terminal half-life is generally in the range of 10 to 60 hours. However, early plasma levels fall quickly, reaching 10% of peak values within 3 and 8 hours after intravenous or oral administration, respectively.

Total clearance of ibandronate is low, with average values in the range 84 to 160 mL/min. Renal clearance (about 60 mL/min in healthy postmenopausal females) accounts for 50% to 60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances likely reflects bone uptake of the drug.

Special Populations

Pediatrics

The pharmacokinetics of ibandronate has not been studied in patients <18 years of age.

Gender

The bioavailability and pharmacokinetics of ibandronate are similar in both men and women.

Geriatric

Since ibandronate is not known to be metabolized, the only difference in ibandronate elimination for geriatric patients versus younger patients is expected to relate to progressive age-related changes in renal function (see Special Populations: **Renal Impairment**).

Race

Pharmacokinetic differences due to race have not been studied.

Renal Impairment

Renal clearance of ibandronate in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr).

Following a single dose of 0.5 mg ibandronate by intravenous administration, patients with CLcr 40 to 70 mL/min had 55% higher exposure (AUC_∞) than the exposure observed in subjects with CLcr >90 mL/min. Patients with CLcr <30 mL/min had more than a two-fold increase in exposure compared to the exposure for healthy subjects (see DOSAGE AND ADMINISTRATION: **Patients with Renal Impairment**).

Hepatic Impairment

No studies have been performed to assess the pharmacokinetics of ibandronate in patients with hepatic impairment since ibandronate is not metabolized in the human liver.

Drug Interactions

Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. Ibandronate is eliminated by renal excretion. Based on a rat study, the ibandronate secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other drugs.

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron), including milk, food, and antacids are likely to interfere with absorption of ibandronate, which is consistent with findings in animal studies.

H2 Blockers and Proton Pump Inhibitors (PPIs)

A pharmacokinetic interaction study in healthy volunteers demonstrated that 75 mg ranitidine (25 mg injected intravenously 90 and 15 minutes before and 30 minutes after ibandronate administration) increased the oral bioavailability of 10 mg ibandronate by about 20%. This degree of increase is not considered to be clinically relevant.

Tamoxifen

A pharmacokinetic interaction study in healthy postmenopausal women demonstrated that there was no interaction between oral 30 mg tamoxifen and intravenous 2 mg ibandronate.

Pharmacodynamics

Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist. The diagnosis can be confirmed by a finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. While osteoporosis occurs in both men and women, it is most common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture during their remaining lifetimes.

BONIVA produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked C-telopeptide of type I collagen) in the daily dose range of 0.25 to 5.0 mg in postmenopausal women.

Treatment with 2.5 mg daily BONIVA resulted in decreases in biochemical markers of bone turnover, including urinary C-terminal telopeptide of type 1 collagen (uCTX) and serum osteocalcin, to levels similar to those in premenopausal women. Changes in markers of bone formation were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and formation. Treatment with 2.5 mg daily BONIVA decreased levels of uCTX within 1 month of starting treatment and decreased levels of osteocalcin within 3 months. Bone turnover markers reached a nadir of approximately 64% below baseline values by 6 months of treatment and remained stable with continued treatment for up to 3 years.

Following treatment discontinuation, there is a return to pretreatment baseline rates of elevated bone resorption associated with postmenopausal osteoporosis.

Clinical Studies

Treatment of Postmenopausal Osteoporosis

Effect on Vertebral Fracture

The effectiveness and safety of BONIVA were demonstrated in a randomized, double-blind, placebo-controlled, multinational study (Treatment Study) of 2946 women aged 55 to 80 years, who were on average 21 years post-menopause, who had lumbar spine BMD 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. BONIVA was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently. The main outcome measure was the occurrence of new radiographically diagnosed, vertebral fractures after 3 years of treatment. The diagnosis of an incident vertebral fracture was based on both qualitative diagnosis by the radiologist and quantitative morphometric criterion. The morphometric criterion required the dual occurrence of 2 events: a relative height ratio or relative height reduction in a vertebral body of at least 20%, together with at least a 4 mm absolute decrease in height. All women received 400 IU vitamin D and 500 mg calcium supplementation per day.

BONIVA 2.5 mg daily significantly reduced the incidence of new vertebral and of new and worsening vertebral fractures. Over the course of the 3-year study, the risk for vertebral fracture was 9.6% in the placebo-treated women and 4.7% in the women treated with BONIVA 2.5 mg ($p<0.001$) (see Table 1).

Table 1 Effect of BONIVA on the Incidence of Vertebral Fracture in the Three-Year Osteoporosis Treatment Study*

	Proportion of Patients with Fracture (%)			
	Placebo n=975	BONIVA 2.5 mg daily n=977	Absolute Risk Reduction (%) 95% CI	Relative Risk Reduction (%) 95% CI
New Vertebral Fracture 0-3 Year	9.6	4.7	4.9 (2.3, 7.4)	52** (29, 68)
New and Worsening Vertebral Fracture 0-3 Year	10.4	5.1	5.3 (2.6, 7.9)	52 (30, 67)
Clinical (Symptomatic) Vertebral Fracture 0-3 Year	5.3	2.8	2.5 (0.6, 4.5)	49 (14, 69)

*The endpoint value is the value at the study's last time point, 3 years, for all patients who had a fracture identified at that time; otherwise, the last post-baseline value prior to the study's last time point is used.
**p=0.0003 vs. placebo

Effect on Nonvertebral Fractures

There was a similar number of nonvertebral osteoporotic fractures reported in women treated with BONIVA [9.1%, (CI: 7.1%, 11.1%)] and placebo [8.2%, (CI: 6.3%, 10.2%)]. The two treatment groups were also similar with regard to the number of fractures reported at the individual non-vertebral sites: pelvis, femur, wrist, forearm, rib, and hip.

Effect on Bone Mineral Density (BMD)

BONIVA significantly increased BMD at the lumbar spine and hip relative to treatment with placebo. In the 3-year osteoporosis treatment study, BONIVA 2.5 mg produced increases in lumbar spine BMD that were progressive over 3 years of treatment and were statistically significant relative to placebo at 6 months and at all later timepoints. Lumbar spine BMD increased by 6.4% after 3 years of treatment with 2.5 mg daily BONIVA compared with 1.4 % in the placebo group. Table 2 displays the significant increases in BMD seen at the lumbar spine, total hip, femoral neck, and trochanter compared to placebo. Thus, overall BONIVA reverses the loss of BMD, a central factor in the progression of osteoporosis.

Table 2 Mean Percent Change in BMD from Baseline to Endpoint in Patients Treated with BONIVA 2.5mg or Placebo in the 3-Year Osteoporosis Treatment Study*

	Placebo	BONIVA 2.5 mg
Lumbar spine	1.4 (n = 693)	6.4 (n = 712)
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)

*The endpoint value is the value at the study's last time point, 3 years, for all patients who had BMD measured at that time; otherwise the last post-baseline value prior to the study's last time point is used.

Bone Histology

The effects of BONIVA 2.5 mg daily on bone histology were evaluated in iliac crest biopsies from 16 women after 22 months of treatment and 20 women after 34 months of treatment.

The histological analysis of bone biopsies showed bone of normal quality and no indication of osteomalacia or a mineralization defect.

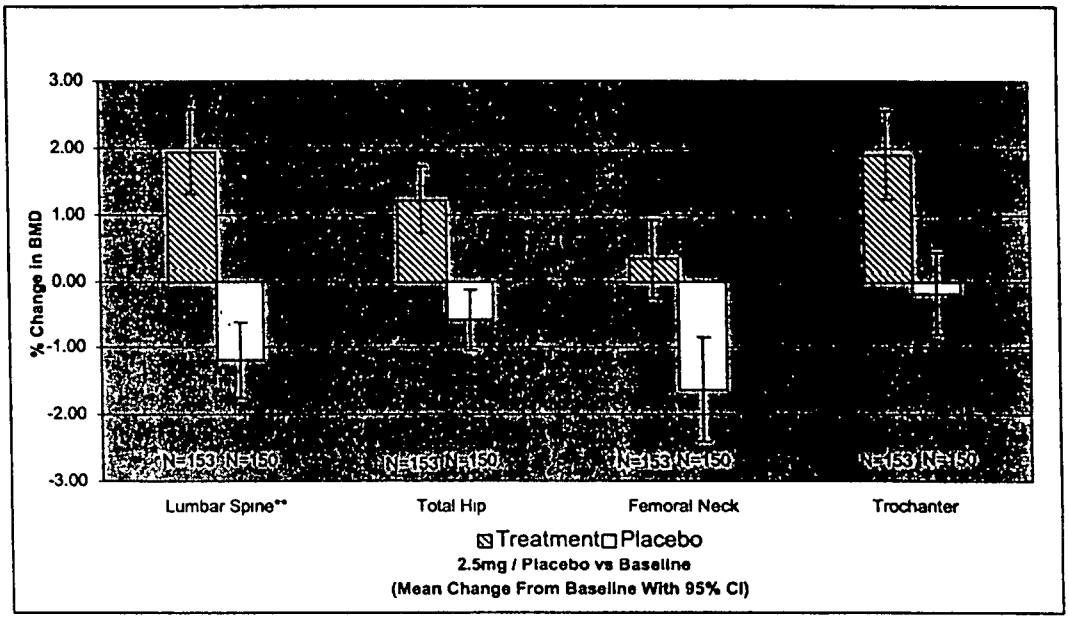
Prevention of Postmenopausal Osteoporosis

BONIVA 2.5 mg prevented bone loss in a majority of women in a randomized, double-blind, placebo-controlled 2-year study (Prevention Study) of 653 postmenopausal women without osteoporosis at baseline. Women were aged 41 to 82 years, were on average 8.5 years post-menopause, and had lumbar spine BMD T-scores >-2.5. Women were stratified according to time since menopause (1 to 3 years, >3 years) and baseline lumbar spine BMD (T score:>-1, -1 to -2.5). The study compared daily BONIVA at three dose levels (0.5 mg, 1.0 mg, 2.5 mg) with placebo. All women received 500 mg of supplemental calcium per day.

The primary efficacy measure was the change in BMD of lumbar spine after 2 years of treatment. BONIVA 2.5 mg daily resulted in a mean increase in lumbar spine BMD of 3.1% compared with placebo following 2 years of treatment (see Figure 1). Increases in BMD were seen at 6 months and at all later timepoints. Irrespective of the time since menopause or the degree of pre-existing bone loss, treatment with BONIVA resulted in a higher BMD response at the lumbar spine compared with placebo across all four baseline strata [time since menopause (1-3 years, > 3 years) and baseline lumbar spine BMD (T score:>-1, -1 to -2.5)].

Compared with placebo, treatment with BONIVA 2.5 mg daily increased BMD of the total hip by 1.8%, the femoral neck by 2.0%, and the trochanter by 2.1% (see Figure 1).

Figure 1 Mean Percentage Change in BMD from Baseline to Endpoint in Patients Treated with BONIVA 2.5 mg or Placebo in the Two-Year Osteoporosis Prevention Study*



*The endpoint value is the value at the study's last time point, 2 years, for all patients who had BMD measured at that time; otherwise the last post-baseline value prior to the study's last time point is used

**lumbar spine BMD $p<0.001$ vs. placebo

Animal Pharmacology

Animal studies have shown that ibandronate is an inhibitor of osteoclast-mediated bone resorption. In the Schenk assay in growing rats, ibandronate inhibited bone resorption and increased bone volume, based on histologic examination of the tibial metaphyses. There was no evidence of impaired mineralization at the highest dose of 5 mg/kg/day (subcutaneously), which is 1000 times the lowest antiresorptive dose of 0.005 mg/kg/day in this model, and 5000 times the optimal antiresorptive dose of 0.001 mg/kg/day in the aged ovariectomized rat. This indicates that BONIVA administered at therapeutic doses is unlikely to induce osteomalacia.

Long-term daily or intermittent administration of ibandronate to ovariectomized rats or monkeys was associated with suppression of bone turnover and increases in bone mass. Vertebral BMD, trabecular density, and biomechanical strength were increased dose-dependently in rats and monkeys, at doses up to 15 times the human oral 2.5 mg/day dose, based on body surface area (mg/m^2) or AUC comparison. Ibandronate maintained the positive correlation between bone mass and strength at the ulna and femoral neck. New bone formed in the presence of ibandronate had normal histologic structure and did not show mineralization defects.

INDICATIONS AND USAGE

BONIVA is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

Treatment of Osteoporosis

In postmenopausal women with osteoporosis, BONIVA increases BMD and reduces the incidence of vertebral fractures (see CLINICAL STUDIES). Osteoporosis may be confirmed by the presence or history of osteoporotic fracture or by a finding of low bone mass (BMD more than 2 standard deviations below the premenopausal mean [i.e., T score]).

Prevention of Osteoporosis

BONIVA may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

Factors such as family history of osteoporosis, early menopause, previous fracture, high bone turnover, reduced BMD (at least 1.0 SD below the premenopausal mean), thin body frame, Caucasian or Asian race, and smoking, are associated with an increased risk of developing osteoporosis and fractures. The presence of these risk factors may be important when considering the use of BONIVA for preventing osteoporosis.

CONTRAINDICATIONS

- Known hypersensitivity to BONIVA or to any of its excipients
- Uncorrected hypocalcemia (see PRECAUTIONS: General)
- Inability to stand or sit upright for at least 60 minutes (see DOSAGE and ADMINISTRATION)

WARNINGS

BONIVA, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer (see PRECAUTIONS).

PRECAUTIONS

General

Mineral Metabolism

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting BONIVA therapy. Adequate intake of calcium and vitamin D is important in all patients.

Upper Gastrointestinal Effects

Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. This association has been reported for bisphosphonates in postmarketing experience but has not been found in most preapproval clinical trials, including those conducted with BONIVA. Therefore, patients should be advised to pay particular attention to and be able to comply with the dosing instructions to minimize the risk of these effects (see DOSAGE AND ADMINISTRATION).

Severe Renal Impairment

BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).

Information for Patients

Patients should be instructed to read the Patient Information Leaflet carefully before taking BONIVA, to re-read it each time the prescription is renewed and to pay particular attention to the dosing instructions in order to maximize absorption and clinical benefit.

- BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day and before any oral medications containing multivalent cations (including antacids, supplements or vitamins).
- To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA.
- Plain water is the only drink that should be taken with BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. Intake of supplemental calcium and vitamin D should be delayed for at least 60 minutes following oral administration of BONIVA in order to maximize absorption of BONIVA.

Physicians should be alert to signs or symptoms signaling a possible esophageal reaction during therapy, and patients should be instructed to discontinue BONIVA and seek medical attention if they develop symptoms of esophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

Drug Interactions

See CLINICAL PHARMACOLOGY: Pharmacokinetics: Drug Interactions

Calcium Supplements/Antacids

Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of BONIVA. BONIVA should be taken at least 60 minutes before any oral medications containing multivalent cations (including antacids, supplements or vitamins) (see PRECAUTIONS: Information for Patients).

H2 Blockers and Proton Pump Inhibitors (PPIs)

Of over 3500 patients enrolled in the BONIVA osteoporosis Treatment and Prevention Studies, 15% used anti-peptic agents (primarily H2 blockers and PPIs). Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with BONIVA was similar to that in placebo-treated patients.

Aspirin/Nonsteroidal Antiinflammatory Drugs (NSAIDs)

In the large, placebo-controlled osteoporosis Treatment Study, aspirin and nonsteroidal antiinflammatory drugs were taken by 62% of the 2946 patients. Among aspirin or NSAID users, the incidence of upper gastrointestinal adverse events in patients treated with ibandronate 2.5 mg daily (28.9%) was similar to that

in placebo-treated patients (30.7%). However, since aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with BONIVA.

Drug/Laboratory Test Interactions

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to Wistar rats (systemic exposures in males and females up to 12 and 7 times, respectively, human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to NMRI mice (exposures in males and females up to 475 and 70 times, respectively, human exposure at the recommended dose of 2.5 mg/day, based on AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice. A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (220 to 400 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). The relevance of these findings to humans is unknown.

Mutagenesis

There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: in vitro bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the in vivo mouse micronucleus tests for chromosomal damage.

Impairment of Fertility

In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed at an oral dose of 16 mg/kg/day (45 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison).

Pregnancy

Pregnancy Category C

In female rats given oral doses of 1, 4, or 16 mg/kg/day beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups (≥3 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison) was likely related to maternal dystocia. In pregnant rats given oral doses of 6, 20, or 60 mg/kg/day during gestation, calcium supplementation (32 mg/kg/day by subcutaneous injection from gestation day 18 to parturition) did not completely prevent dystocia and periparturient mortality in any of

the treated groups (≥16 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). A low incidence of postimplantation loss was observed in rats treated from 14 days before mating throughout lactation or during gestation only, at doses causing maternal dystocia and periparturient mortality. In pregnant rats dosed orally with 1, 5, or 20 mg/kg/day from gestation day 17 through lactation day 21 (following closure of the hard palate through weaning), maternal toxicity, including dystocia and mortality, and perinatal and postnatal pup mortality were observed at doses ≥5 mg/kg/day (equivalent to human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia.

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses ≥10 mg/kg/day (≥30 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison). Impaired pup neuromuscular development (cliff avoidance test) was observed at 16 mg/kg/day when dams were dosed from 14 days before mating through lactation (45 times human exposure at the recommended oral dose of 2.5 mg/day, based on AUC comparison).

In pregnant rabbits given oral doses of 1, 4, or 20 mg/kg/day during gestation, dose-related maternal mortality was observed in all treatment groups (≥8 times the recommended human oral dose of 2.5 mg/day, based on body surface area comparison, mg/m^2). The deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed.

There are no adequate and well-controlled studies in pregnant women. BONIVA should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/mL from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BONIVA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the patients receiving BONIVA in postmenopausal osteoporosis studies, 52% were over 65 years of age, and 10% were over 75 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS

Oral BONIVA has been studied in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily in these studies was similar to that of placebo.

Treatment and Prevention of Postmenopausal Osteoporosis

Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg group and the placebo group. Overall, and according to body system, there was no difference between BONIVA and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

Table 3 lists adverse events from the Treatment and Prevention Studies reported in ≥2% of patients and in more patients treated with BONIVA than patients treated with placebo. Adverse events are shown without attribution of causality.

Table 3 Adverse Events Occurring at a Frequency ≥2% and in More Patients Treated with BONIVA than in Patients Treated with Placebo in the Osteoporosis Treatment and Prevention Studies

Body System	Placebo % (n=1134)	BONIVA 2.5mg % (n=1140)
Body as a Whole		
Back Pain	12.2	13.5
Pain in Extremity	6.4	7.8
Infection	3.4	4.3
Asthenia	2.3	3.5
Allergic Reaction	1.9	2.5
Digestive System		
Dyspepsia	9.8	11.9
Diarrhea	5.0	6.8
Tooth Disorder	2.3	3.5
Vomiting	2.1	2.7
Gastritis	1.9	2.2
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.2	4.8
Musculoskeletal System		
Myalgia	5.1	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
Nervous System		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
Respiratory System		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
Urogenital System		
Urinary Tract Infection	4.2	5.5

Ocular Adverse Events

Although not reported in the pre-approval trials of oral ibandronate, reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued.

Laboratory Test Findings

There were no clinically significant changes from baseline values or shifts in any laboratory variable for each of the treatment groups. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen in the active treatment groups compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia.

OVERDOSAGE

No specific information is available on the treatment of overdosage with BONIVA. However, based on knowledge of this class of compounds, oral overdosage may result in hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, dyspepsia, esophagitis, gastritis, or ulcer. Milk or antacids should be given to bind BONIVA. Due to the risk of esophageal irritation, vomiting should not be induced, and the patient should remain fully upright. Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

The recommended dose of BONIVA for treatment and prevention of postmenopausal osteoporosis is one 2.5 mg film-coated tablet once daily (see INDICATIONS AND USAGE).

- To maximize absorption and clinical benefit, BONIVA should be taken at least 60 minutes before the first food or drink (other than water) of the day or any oral medication or supplementation, including calcium, antacids, or vitamins (see PRECAUTIONS: Information for Patients and Drug Interactions).
- To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, BONIVA tablets should be swallowed whole with a full glass of plain water (6 to 8 oz) while the patient is standing or sitting in an upright position. Patients should not lie down for 60 minutes after taking BONIVA (see PRECAUTIONS: General and Information for Patients).
- Plain water is the only drink that should be taken with BONIVA. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.

Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate. (see PRECAUTIONS: Information for Patients).

Patients with Hepatic Impairment

No dose adjustment is necessary (see CLINICAL PHARMACOLOGY: Special Populations).

Patients with Renal Impairment

No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 mL/min.

BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance of <30 mL/min) (see CLINICAL PHARMACOLOGY: Special Populations).

Geriatric Patients

No dosage adjustment is necessary in the elderly (see PRECAUTIONS: Geriatric Use).

HOW SUPPLIED

BONIVA 2.5 mg tablets: supplied as white, oblong, film-coated tablets, engraved with "RO" on one side and "L3" on the other side and packaged in bottles of 30 tablets (NDC 0004-0185-23), bottles of 90 tablets (NDC 0004-0185-52), and bottles of 500 tablets (NDC 0004-0185-14).

Storage

Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

R_X only

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Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

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Patient Information

BONIVA™ [bon-EE-va]
(ibandronate sodium)
TABLETS

Read this patient information carefully before you start taking BONIVA. Read this patient information each time you get a refill for BONIVA. There may be new information. This information does not take the place of talking with your health care provider about your condition or your treatment. Talk about BONIVA with your health care provider before you start taking it, and at your regular check-ups.

What is the most important information I should know about BONIVA?

BONIVA may cause serious problems in the stomach and the esophagus (the tube that connects your mouth and stomach) such as trouble swallowing, heartburn, and ulcers (see **"What are the possible side effects of BONIVA?"**).

You must take BONIVA exactly as prescribed for BONIVA to work for you and to lower the chance of serious side effects (see "How should I take BONIVA?").

What is BONIVA?

BONIVA is a prescription medicine used to treat or prevent osteoporosis in women after menopause (see the end of this leaflet for **"What is osteoporosis?"**).

BONIVA may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they won't be able to see or feel a difference. BONIVA may help lower the chances of breaking bones (fractures).

For BONIVA to treat or prevent osteoporosis, you have to take it as prescribed. BONIVA will not work if you stop taking it.

Who should not take BONIVA?

Do not take BONIVA if you:

- have low blood calcium (hypocalcemia)
- cannot sit or stand up for at least 1 hour (60 minutes)
- have kidneys that work very poorly
- are allergic to ibandronate sodium or any of the other ingredients of BONIVA (see the end of this leaflet for a list of all the ingredients in BONIVA)

Tell your health care provider before using BONIVA:

- if you are pregnant or planning to become pregnant. It is not known if BONIVA can harm your unborn baby.
- if you are breast-feeding. It is not known if BONIVA passes into your milk and if it can harm your baby.
- have swallowing problems or other problems with your esophagus (the tube that connects your mouth and stomach)
- if you have kidney problems
- **about all the medicines you take** including prescription and non-prescription medicines, vitamins and supplements. Some medicines, especially certain vitamins, supplements, and antacids can stop BONIVA from getting to your bones. This can happen if you take other medicines too close to the time that you take BONIVA (see **"How should I take BONIVA?"**).

How should I take BONIVA?

- Take BONIVA exactly as instructed by your health care provider.
- Take BONIVA first thing in the morning at least 1 hour (60 minutes) before you eat, drink anything other than plain water, or take any other medicine.
- Take BONIVA with 6 to 8 ounces (about 1 full cup) of plain water. Do not take it with any other drink besides plain water. Do not take it with other drinks, such as mineral water, sparkling water, coffee, tea, dairy drinks (such as milk), or juice.
- Swallow BONIVA whole. Do not chew the tablet or keep it in your mouth to melt or dissolve.
- After taking BONIVA you must wait at least 1 hour (60 minutes) before:
- Lying down. You may sit, stand, or do normal activities like read the newspaper or take a walk.
- Eating or drinking anything except for plain water.
- Taking other medicines including vitamins, calcium, or antacids. Take your vitamins, calcium, and antacids at a different time of the day from the time when you take BONIVA.
- If you forget to take your BONIVA in the morning, **do not** take it later in the day. Just return to your normal schedule and take 1 tablet the next morning. **Do not** take two tablets on the same day.
- If you take too much BONIVA, drink a full glass of milk and call your local poison control center or emergency room right away. Do not make yourself vomit. Do not lie down.
- Keep taking BONIVA for as long as your health care provider tells you. BONIVA will not work if you stop taking it.
- Your health care provider may tell you to exercise and take calcium and vitamin supplements to help your osteoporosis.
- Your health care provider may do a test to measure the thickness (density) of your bones or do other tests to check your progress.

What should I avoid while taking BONIVA?

- Do not take other medicines, or eat or drink anything but plain water before you take BONIVA and for at least 1 hour (60 minutes) after you take it.
- Do not lie down for at least 1 hour (60 minutes) after you take BONIVA.

What are the possible side effects of BONIVA?

Stop taking BONIVA and call your health care provider right away if you have:

- **pain or trouble with swallowing**
- **chest pain**
- **very bad heartburn or heartburn that does not get better**

BONIVA may cause:

- pain or trouble swallowing (dysphagia)
- heartburn (esophagitis)
- ulcers in your stomach or esophagus (the tube that connects your mouth and stomach)

Common side effects with BONIVA are:

- diarrhea
- pain in extremities (arms or legs)
- dyspepsia (upset stomach)

These are not all the possible side effects of BONIVA. For more information ask your health care provider or pharmacist.

What is osteoporosis?

Osteoporosis is a disease that causes bones to become thinner. Thin bones can break easily. Most people think of their bones as being solid like a rock. Actually, bone is living tissue, just like other parts of the body, such as your heart, brain, or skin. Bone just happens to be a harder type of tissue. Bone is always changing. Your body keeps your bones strong and healthy by replacing old bone with new bone.

Osteoporosis causes the body to remove more bone than it replaces. This means that bones get weaker. Weak bones are more likely to break. Osteoporosis is a bone disease that is quite common in women after menopause. At first, osteoporosis has no symptoms, but people with osteoporosis may develop loss of height and are more likely to break (fracture) their bones, especially the back (spine), wrist, and hip bones.

Osteoporosis can be prevented, and with proper therapy it can be treated.

Who is at risk for osteoporosis?

Talk to your health care provider about your chances for getting osteoporosis.

Many things put people at risk for osteoporosis. The following people have a higher chance of getting osteoporosis:

Women who:

- are going through or who are past menopause ("the change")
- are white (Caucasian) or Oriental (Asian)

People who:

- are thin
- have a family member with osteoporosis
- do not get enough calcium or vitamin D
- do not exercise
- smoke
- drink alcohol often
- take bone thinning medicines (like prednisone) for a long time

General information about BONIVA

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use BONIVA for a condition for which it was not prescribed. Do not give BONIVA to other people, even if they have the same symptoms you have. It may harm them.

Store BONIVA at 77 °F (25°C) or at room temperature between 59° and 86°F (15° and 30°C).

Keep BONIVA and all medicines out of the reach of children.

This leaflet summarizes the most important information about BONIVA. If you would like more

information, talk with your health care provider. You can ask your health care provider or pharmacist for information about BONIVA that is written for health professionals.

For more information about BONIVA, call 1-800-xxx-xxxx or visit www.xxxxxx.com.

What are the ingredients of BONIVA?

BONIVA (active ingredient): ibandronate sodium

BONIVA (inactive ingredients): lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000 and purified water.

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