Addendum to the

Background Document for Meeting of
Advisory Committee for Reproductive Health Drugs
and
Drug Safety and Risk Management Advisory Committee

Prepared by
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September 9, 2011

For reference, this addendum to the background document for the joint meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee contains the product labeling for the bisphosphonates approved for the treatment of osteoporosis. This addendum contains the most updated labeling as of August 31, 2011. No further labeling updates are anticipated prior to the September 9, 2011 meeting.

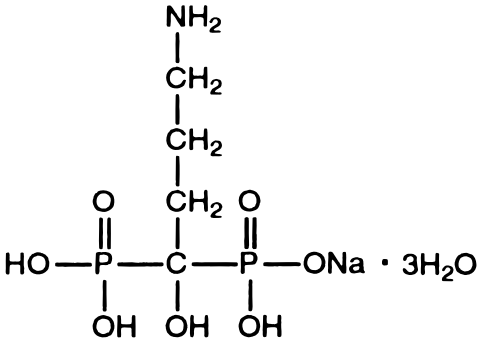
FOSAMAX®
(ALENDRONATE SODIUM) TABLETS AND ORAL SOLUTION

DESCRIPTION

FOSAMAX® (alendronate sodium) is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.

The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is

not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: The oral bioavailability in children was similar to that observed in adults; however, FOSAMAX is not indicated for use in children (see PRECAUTIONS, *Pediatric Use*).

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.**

Hepatic Insufficiency: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions (also see PRECAUTIONS, *Drug Interactions*)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. In osteoporosis prevention studies FOSAMAX 5 mg/day decreased osteocalcin and total serum alkaline phosphatase by approximately 40% and 15%, respectively. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly FOSAMAX 70 mg for the treatment of osteoporosis and once weekly FOSAMAX 35 mg for the prevention of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. Similar reductions were observed with FOSAMAX 5 mg/day. In one-year studies with once weekly FOSAMAX 35 and 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Osteoporosis in men

Treatment of men with osteoporosis with FOSAMAX 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly FOSAMAX 70 mg.

Glucocorticoid-induced Osteoporosis

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs both in males and females of all ages. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Alendronate decreases bone resorption without directly inhibiting bone formation.

In clinical studies of up to two years' duration, FOSAMAX 5 and 10 mg/day reduced cross-linked N-telopeptides of type I collagen (a marker of bone resorption) by approximately 60% and reduced bone-specific alkaline phosphatase and total serum alkaline phosphatase (markers of bone formation) by approximately 15 to 30% and 8 to 18%, respectively. As a result of inhibition of bone resorption, FOSAMAX 5 and 10 mg/day induced asymptomatic decreases in serum calcium (approximately 1 to 2%) and serum phosphate (approximately 1 to 8%).

Paget's disease of bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

FOSAMAX decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX 40 mg once daily for six months produced significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, FOSAMAX induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of osteoporosis

Postmenopausal women

Effect on bone mineral density

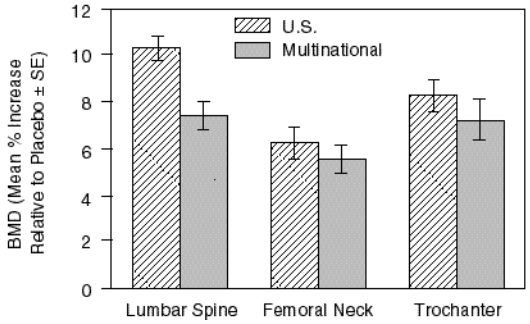
The efficacy of FOSAMAX 10 mg once daily in postmenopausal women, 44 to 84 years of age, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. The following graph shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to placebo-treated patients at three years for each of these studies.

(n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70-mg once-weekly group (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard

Reference ID: 2895752

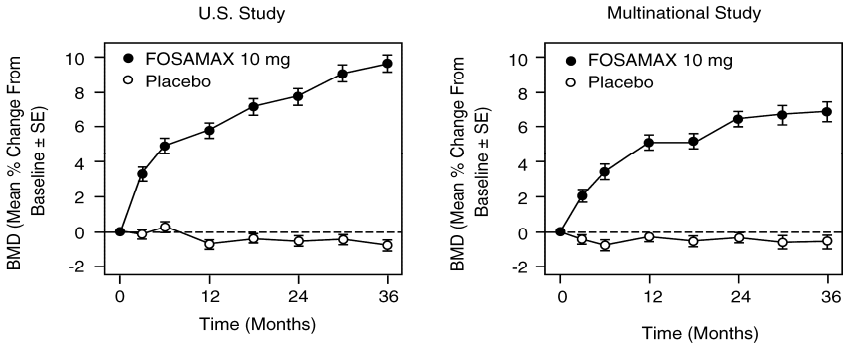
Osteoporosis Treatment Studies in Postmenopausal Women

Increase in BMD
FOSAMAX 10 mg/day at Three Years



Osteoporosis Treatment Studies in Postmenopausal Women

Time Course of Effect of FOSAMAX 10 mg/day Versus Placebo:
Lumbar Spine BMD Percent Change From Baseline



to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Effect on fracture incidence

Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies: 1) U.S. and Multinational combined: a study of patients with a BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.

To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), the U.S. and Multinational studies were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in the table below.

Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT
(patients with vertebral fracture at baseline)

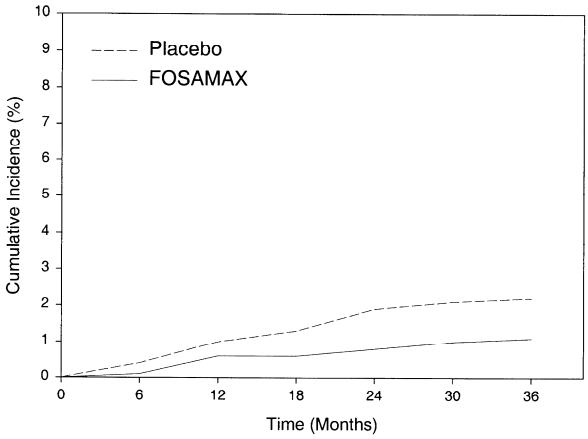
	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)[†]				
≥ 1 new vertebral fracture	7.9	15.0	7.1	47***
≥ 2 new vertebral fractures	0.5	4.9	4.4	90***
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26[‡]
≥ 1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54**
Hip fracture	1.1	2.2	1.1	51*
Wrist (forearm) fracture	2.2	4.1	1.9	48*

[†]Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
*p<0.05, **p<0.01, ***p<0.001, [‡]p=0.007

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. The figure below displays the cumulative incidence of hip fractures in this study.

Cumulative Incidence of Hip Fractures in the
Three-Year Study of FIT
(patients with radiographic vertebral fracture at baseline)



Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in the table below for the patients with osteoporosis.

Effect of FOSAMAX on Fracture Incidence in Osteoporotic† Patients in the Four-Year Study of FIT
(patients without vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)††				
≥ 1 new vertebral fracture	2.5	4.8	2.3	48***
≥ 2 new vertebral fractures	0.1	0.6	0.5	78*
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22**
≥ 1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)†††
Hip fracture	1.0	1.4	0.4	29 (NS)†††
Wrist (forearm) fracture	3.9	3.8	-0.1	NS†††

†Baseline femoral neck BMD at least 2 SD below the mean for young adult women
††Number evaluable for vertebral fractures: FOSAMAX, n=1426; placebo, n=1428
†††Not significant. This study was not powered to detect differences at these sites.
*p=0.035, ** p=0.01, ***p<0.001

Fracture results across studies

In the Three-Year Study of FIT, FOSAMAX reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p<0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction,

p=0.001); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p=0.034).

FOSAMAX reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p<0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, p<0.001) in the Three-Year Study of FIT. In the Four-Year Study of FIT, FOSAMAX reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, p=0.035).

Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.

FOSAMAX, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.

Bone histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with FOSAMAX is of normal quality.

Men

The efficacy of FOSAMAX in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.

A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, -0.6 mm vs. placebo, -2.4 mm).

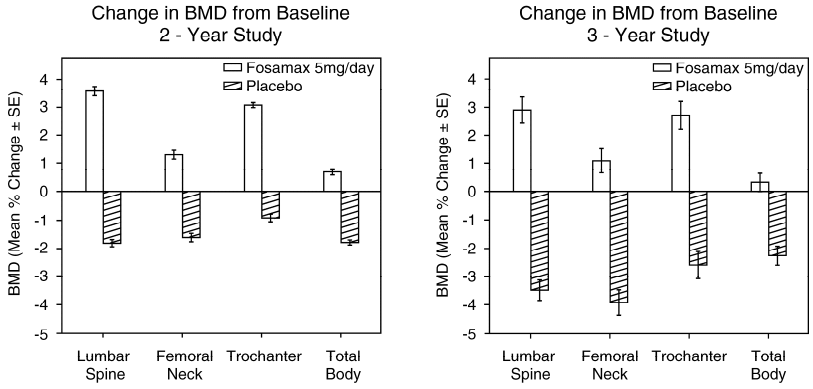
A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.

In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL vs. ≥9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >-2.5).

Prevention of osteoporosis in postmenopausal women

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal women 40-60 years of age. One thousand six hundred nine patients (FOSAMAX 5 mg/day; n=498) who were at least six months postmenopausal were entered into a two-year study without regard to their baseline BMD. In the other study, 447 patients (FOSAMAX 5 mg/day; n=88), who were between six months and three years postmenopause, were treated for up to three years. In the placebo-treated patients BMD losses of approximately 1% per year were seen at the spine, hip (femoral neck and trochanter) and total body. In contrast, FOSAMAX 5 mg/day prevented bone loss in the majority of patients and induced significant increases in mean bone mass at each of these sites (see figures below). In addition, FOSAMAX 5 mg/day reduced the rate of bone loss at the forearm by approximately half relative to placebo. FOSAMAX 5 mg/day was similarly effective in this population regardless of age, time since menopause, race and baseline rate of bone turnover.

Osteoporosis Prevention Studies in Postmenopausal Women



The therapeutic equivalence of once weekly FOSAMAX 35 mg (n=362) and FOSAMAX 5 mg daily (n=361) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women without osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 2.9% (2.6, 3.2%; 95% CI) in the 35-mg once-weekly group (n=307) and 3.2% (2.9, 3.5%; 95% CI) in the 5-mg daily group (n=298). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone histology

Bone histology was normal in the 28 patients biopsied at the end of three years who received FOSAMAX at doses of up to 10 mg/day.

Concomitant use with estrogen/hormone replacement therapy (HRT)

The effects on BMD of treatment with FOSAMAX 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or FOSAMAX alone (both 6.0%).

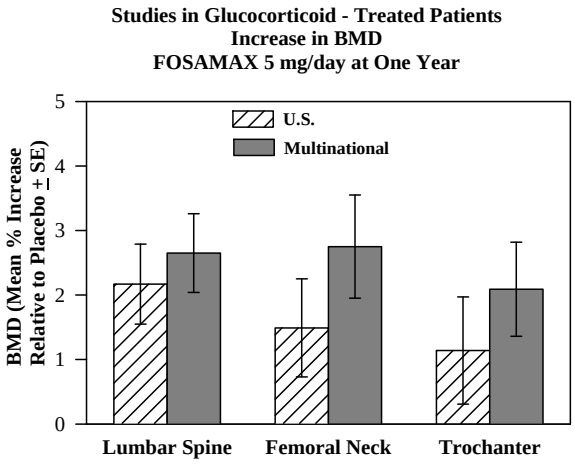
The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).

In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.

Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied.

Glucocorticoid-induced osteoporosis

The efficacy of FOSAMAX 5 and 10 mg once daily in men and women receiving glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) was demonstrated in two, one-year, double-blind, randomized, placebo-controlled, multicenter studies of virtually identical design, one performed in the United States and the other in 15 different countries (Multinational [which also included FOSAMAX 2.5 mg/day]). These studies enrolled 232 and 328 patients, respectively, between the ages of 17 and 83 with a variety of glucocorticoid-requiring diseases. Patients received supplemental calcium and vitamin D. The following figure shows the mean increases relative to placebo in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 5 mg/day for each study.



After one year, significant increases relative to placebo in BMD were seen in the combined studies at each of these sites in patients who received FOSAMAX 5 mg/day. In the placebo-treated patients, a significant decrease in BMD occurred at the femoral neck (-1.2%), and smaller decreases were seen at the lumbar spine and trochanter. Total body BMD was maintained with FOSAMAX 5 mg/day. The increases in BMD with FOSAMAX 10 mg/day were similar to those with FOSAMAX 5 mg/day in all patients except for postmenopausal women not receiving estrogen therapy. In these women, the increases (relative to placebo) with FOSAMAX 10 mg/day were greater than those with FOSAMAX 5 mg/day at the lumbar spine (4.1% vs. 1.6%) and trochanter (2.8% vs. 1.7%), but not at other sites. FOSAMAX was effective regardless of dose or duration of glucocorticoid use. In addition, FOSAMAX was similarly effective regardless of age (<65 vs. ≥65 years), race (Caucasian vs. other races), gender, underlying disease, baseline BMD, baseline bone turnover, and use with a variety of common medications.

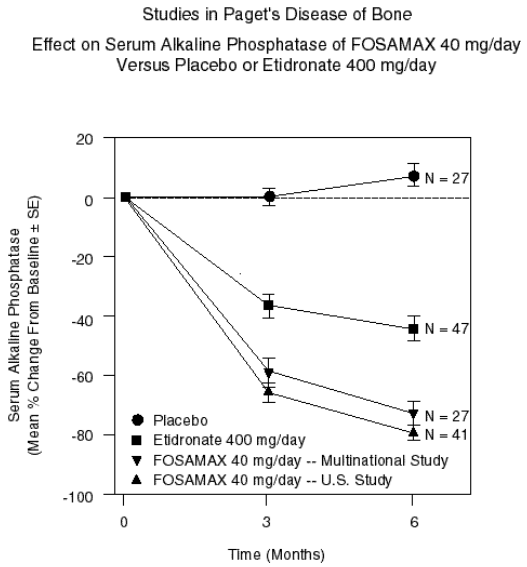
Bone histology was normal in the 49 patients biopsied at the end of one year who received FOSAMAX at doses of up to 10 mg/day.

Of the original 560 patients in these studies, 208 patients who remained on at least 7.5 mg/day of prednisone or equivalent continued into a one-year double-blind extension. After two years of treatment, spine BMD increased by 3.7% and 5.0% relative to placebo with FOSAMAX 5 and 10 mg/day, respectively. Significant increases in BMD (relative to placebo) were also observed at the femoral neck, trochanter, and total body.

After one year, 2.3% of patients treated with FOSAMAX 5 or 10 mg/day (pooled) vs. 3.7% of those treated with placebo experienced a new vertebral fracture (not significant). However, in the population studied for two years, treatment with FOSAMAX (pooled dosage groups: 5 or 10 mg for two years or 2.5 mg for one year followed by 10 mg for one year) significantly reduced the incidence of patients with a new vertebral fracture (FOSAMAX 0.7% vs. placebo 6.8%).

Paget's disease of bone

The efficacy of FOSAMAX 40 mg once daily for six months was demonstrated in two double-blind clinical studies of male and female patients with moderate to severe Paget's disease (alkaline phosphatase at least twice the upper limit of normal): a placebo-controlled, multinational study and a U.S. comparative study with etidronate disodium 400 mg/day. The following figure shows the mean percent changes from baseline in serum alkaline phosphatase for up to six months of randomized treatment.



At six months the suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than that achieved with etidronate and contrasted with the complete lack of response in placebo-treated patients. Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline ≥60%) occurred in approximately 85% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective regardless of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for 6 months. As in patients treated for osteoporosis (see *Clinical Studies, Treatment of osteoporosis in postmenopausal women, Bone histology*), FOSAMAX did not impair mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with FOSAMAX is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX is indicated for:

- Treatment and prevention of osteoporosis in postmenopausal women
    - For the treatment of osteoporosis, FOSAMAX increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*.)

- For the prevention of osteoporosis, FOSAMAX 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 future fracture.

  Bone loss is particularly rapid in postmenopausal women younger than age 60. Risk factors often associated with the development of postmenopausal osteoporosis include early menopause; moderately low bone mass (for example, at least 1 standard deviation below the mean for healthy young adult women); thin body build; Caucasian or Asian race; and family history of osteoporosis. The presence of such risk factors may be important when considering the use of FOSAMAX for prevention of osteoporosis.

- 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 to 7.5 mg or greater of prednisone and who have low bone mineral density (see PRECAUTIONS, *Glucocorticoid-induced osteoporosis*). Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.
- Treatment of Paget's disease of bone in men and women
  - Treatment is indicated in patients with Paget's disease of bone having alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

The safety and effectiveness of FOSAMAX for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes (see WARNINGS)
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution.
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, *General*)

WARNINGS

FOSAMAX, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis, or ulcers).

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates including FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates including FOSAMAX and/or who fail to swallow oral bisphosphonates including FOSAMAX with the recommended full glass (6-8 oz) of water, and/or who continue to take oral bisphosphonates including FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the

patient (see DOSAGE AND ADMINISTRATION). In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

PRECAUTIONS

General

Causes of osteoporosis other than estrogen deficiency, aging, and glucocorticoid use should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

Musculoskeletal Pain

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see ADVERSE REACTIONS). This category of drugs includes FOSAMAX (alendronate). Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

Dental

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including FOSAMAX. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Renal insufficiency

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Glucocorticoid-induced osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established (see INDICATIONS AND USAGE). Before initiating treatment, the hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

The efficacy of FOSAMAX for the treatment of glucocorticoid-induced osteoporosis has been shown in patients with a median bone mineral density which was 1.2 standard deviations below the mean for healthy young adults.

The efficacy of FOSAMAX has been established in studies of two years' duration. The greatest increase in bone mineral density occurred in the first year with maintenance or smaller gains during the second year. Efficacy of FOSAMAX beyond two years has not been studied.

The efficacy of FOSAMAX in respect to fracture prevention has been demonstrated for vertebral fractures. However, this finding was based on very few fractures that occurred primarily in postmenopausal women. The efficacy for prevention of non-vertebral fractures has not been demonstrated.

Information for Patients

General

Physicians should instruct their patients to read the Medication Guide before starting therapy with FOSAMAX and to reread it each time the prescription is renewed.

Patients should be instructed to take supplemental calcium and vitamin D, if daily dietary intake is inadequate. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Absorption*).

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation patients should be instructed to swallow each tablet of FOSAMAX with a full glass of water (6-8 oz). To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral solution. Patients should be instructed not to lie down for at least 30 minutes <u>and</u> until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX and consult their physician.

Patients should be instructed that if they miss a dose of once weekly FOSAMAX, they should take one dose on the morning after they remember. They should not take two doses on the same day but should return to taking one dose once a week, as originally scheduled on their chosen day.

Drug Interactions (also see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drug Interactions*)

Estrogen/hormone replacement therapy (HRT)

Concomitant use of HRT (estrogen ± progestin) and FOSAMAX was assessed in two clinical studies of one or two years' duration in postmenopausal osteoporotic women. In these studies, the safety and tolerability profile of the combination was consistent with those of the individual treatments; however, the degree of suppression of bone turnover (as assessed by mineralizing surface) was significantly greater with the combination than with either component alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence have not been studied (see CLINICAL PHARMACOLOGY, *Clinical Studies*, *Concomitant use with estrogen/hormone replacement therapy (HRT)* and ADVERSE REACTIONS, *Clinical Studies*, *Concomitant use with estrogen/hormone replacement therapy*).

Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX. Therefore, patients must wait at least one-half hour after taking FOSAMAX before taking any other oral medications.

Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

FOSAMAX may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92-week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.12 to 1.2 times a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2-year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 0.26 and 1 times a 40 mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.

Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.

Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (1.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Pregnancy

Pregnancy Category C:

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from 0.26 times (1 mg/kg) to 2.6 times (10 mg/kg) a maximum recommended daily dose of 40 mg (Paget's disease) based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (10.3 times a 40 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (3.9 times a 40 mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.13 times a 40 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

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

Nursing Mothers

It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

The efficacy and safety of FOSAMAX were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4-18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5 mg FOSAMAX daily (weight <40 kg) or 10 mg FOSAMAX daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the FOSAMAX-treated patients and 0.1 in the placebo-treated patients. Treatment with FOSAMAX did not reduce the risk of fracture. Sixteen percent of the FOSAMAX patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In FOSAMAX-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the FOSAMAX and placebo groups in reduction of bone pain.

FOSAMAX is not indicated for use in children.

(For clinical adverse experiences in children, see ADVERSE REACTIONS, *Clinical Studies*, *Osteogenesis Imperfecta*.)

Geriatric Use

Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, osteoporosis studies in men, glucocorticoid-induced osteoporosis studies, and Paget's disease studies (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 45%, 54%, 37%, and 70%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Clinical Studies

In clinical studies of up to five years in duration adverse experiences associated with FOSAMAX usually were mild, and generally did not require discontinuation of therapy.

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Treatment of osteoporosis

Postmenopausal women

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX* % (n=196)	Placebo % (n=397)	FOSAMAX** % (n=3236)	Placebo % (n=3223)
Gastrointestinal				
abdominal pain	6.6	4.8	1.5	1.5
nausea	3.6	4.0	1.1	1.5
dyspepsia	3.6	3.5	1.1	1.2
constipation	3.1	1.8	0.0	0.2
diarrhea	3.1	1.8	0.6	0.3
flatulence	2.6	0.5	0.2	0.3
acid regurgitation	2.0	4.3	1.1	0.9
esophageal ulcer	1.5	0.0	0.1	0.1
vomiting	1.0	1.5	0.2	0.3
dysphagia	1.0	0.0	0.1	0.1
abdominal distention	1.0	0.8	0.0	0.0
gastritis	0.5	1.3	0.6	0.7
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	4.1	2.5	0.4	0.3
muscle cramp	0.0	1.0	0.2	0.1
Nervous System/Psychiatric				
headache	2.6	1.5	0.2	0.2
dizziness	0.0	1.0	0.0	0.1
Special Senses				
taste perversion	0.5	1.0	0.1	0.0

* 10 mg/day for three years
** 5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage, which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 5 or 20 mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5 or 10 mg doses of FOSAMAX in the two-year

extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in the following table.

Osteoporosis Treatment Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	Once Weekly FOSAMAX 70 mg % (n=519)	FOSAMAX 10 mg/day % (n=370)
Gastrointestinal		
abdominal pain	3.7	3.0
dyspepsia	2.7	2.2
acid regurgitation	1.9	2.4
nausea	1.9	2.4
abdominal distention	1.0	1.4
constipation	0.8	1.6
flatulence	0.4	1.6
gastritis	0.2	1.1
gastric ulcer	0.0	1.1
Musculoskeletal		
musculoskeletal (bone, muscle, joint) pain	2.9	3.2
muscle cramp	0.2	1.1

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in the following table.

Osteoporosis Studies in Men
Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients

	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=109)	Placebo % (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience

occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

Osteoporosis Prevention Studies in Postmenopausal Women
Adverse Experiences Considered Possibly, Probably, or
Definitely Drug Related by the Investigators and
Reported in ≥1% of Patients

	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 5 or 10 mg/day or placebo are presented in the following table.

One-Year Studies in Glucocorticoid-Treated Patients
Adverse Experiences Considered Possibly, Probably, or
Definitely Drug Related by the Investigators and
Reported in ≥1% of Patients

	FOSAMAX 10 mg/day % (n=157)	FOSAMAX 5 mg/day % (n=161)	Placebo % (n=159)
Gastrointestinal			
abdominal pain	3.2	1.9	0.0
acid regurgitation	2.5	1.9	1.3
constipation	1.3	0.6	0.0
melena	1.3	0.0	0.0
nausea	0.6	1.2	0.6
diarrhea	0.0	0.0	1.3
Nervous System/Psychiatric			
headache	0.6	0.0	1.3

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Osteogenesis Imperfecta

FOSAMAX is not indicated for use in children.

The overall safety profile of FOSAMAX in OI patients treated for up to 24 months was generally similar to that of adults with osteoporosis treated with FOSAMAX. However, there was an increased occurrence of vomiting in OI patients treated with FOSAMAX compared to placebo. During the 24-month treatment period, vomiting was observed in 32 of 109 (29.4%) patients treated with FOSAMAX and 3 of 30 (10%) patients treated with placebo.

In a pharmacokinetic study, 6 of 24 pediatric OI patients who received a single oral dose of FOSAMAX 35 or 70 mg developed fever, flu-like symptoms, and/or mild lymphocytopenia within 24 to 48 hours after administration. These events, lasting no more than 2 to 3 days and responding to acetaminophen, are consistent with an acute-phase response that has been reported in patients receiving bisphosphonates, including FOSAMAX. See ADVERSE REACTIONS, *Post-Marketing Experience*, *Body as a Whole*.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, *Information for Patients*, and DOSAGE AND ADMINISTRATION).

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection with delayed healing, has been reported rarely (see PRECAUTIONS, *Dental*).

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating (see PRECAUTIONS, Musculoskeletal Pain); joint swelling; low-energy femoral shaft and subtrochanteric fractures (see PRECAUTIONS, Atypical Subtrochanteric and Diaphyseal Femoral Fractures).

Nervous system: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).

No specific information is available on the treatment of overdosage with FOSAMAX. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. 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

FOSAMAX must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only (see PRECAUTIONS, *Information for Patients*). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, *Drug Interactions*). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6-8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes <u>and</u> until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS, PRECAUTIONS, *Information for Patients*).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, *General*).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 70 mg tablet once weekly
  or
- one bottle of 70 mg oral solution once weekly
  or
- one 10 mg tablet once daily

Treatment to increase bone mass in men with osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly
  or
- one bottle of 70 mg oral solution once weekly
  or
- one 10 mg tablet once daily

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE)

The recommended dosage is:

- one 35 mg tablet once weekly
  or

- one 5 mg tablet once daily

The safety of treatment and prevention of osteoporosis with FOSAMAX has been studied for up to 7 years.

Treatment of glucocorticoid-induced osteoporosis in men and women

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

Paget's disease of bone in men and women

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX. Specific retreatment data are not available, although responses to FOSAMAX were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

HOW SUPPLIED

No. 3759 — Tablets FOSAMAX, 5 mg, are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other. They are supplied as follows:

NDC 0006-0925-31 unit-of-use bottles of 30

NDC 0006-0925-58 unit-of-use bottles of 100.

No. 3797 — Tablets FOSAMAX, 10 mg, are white, oval, wax-polished tablets with code MRK on one side and 936 on the other. They are supplied as follows:

NDC 0006-0936-31 unit-of-use bottles of 30

NDC 0006-0936-58 unit-of-use bottles of 100

NDC 0006-0936-28 unit dose packages of 100

NDC 0006-0936-82 bottles of 1,000.

No. 3813 — Tablets FOSAMAX, 35 mg, are white, oval, uncoated tablets with code 77 on one side and a bone image on the other. They are supplied as follows:

NDC 0006-0077-44 unit-of-use blister package of 4

NDC 0006-0077-21 unit dose packages of 20.

No. 8457 — Tablets FOSAMAX, 40 mg, are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other. They are supplied as follows:

NDC 0006-0212-31 unit-of-use bottles of 30.

No. 3814 — Tablets FOSAMAX, 70 mg, are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other. They are supplied as follows:

NDC 0006-0031-44 unit-of-use blister package of 4

NDC 0006-0031-21 unit dose packages of 20.

No. 3833 — Oral Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows:

NDC 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each.

Storage

FOSAMAX Tablets:

Store in a well-closed container at room temperature, 15-30°C (59-86°F).

FOSAMAX Oral Solution:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Do not freeze.

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

FOSAMAX®
(alendronate sodium) Tablets and Oral Solution 6013411

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MEDICATION GUIDE
FOSAMAX® (FOSS-ah-max)
(*alendronate sodium*)
Tablets and Oral Solution

Read the Medication Guide that comes with FOSAMAX® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about FOSAMAX.

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

FOSAMAX can cause serious side effects including:

1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Bone, joint, or muscle pain
4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

1. **Esophagus problems.**
   Some people who take FOSAMAX may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.
   - **It is important that you take FOSAMAX exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take FOSAMAX?")**
   - **Stop taking FOSAMAX and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.**

2. **Low calcium levels in your blood (hypocalcemia).**
   FOSAMAX may lower the calcium levels in your blood. If you have low blood calcium before you start taking FOSAMAX, it may get worse during treatment. Your low blood calcium must be treated before you take FOSAMAX. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:
   - Spasms, twitches, or cramps in your muscles
   - Numbness or tingling in your fingers, toes, or around your mouth

   Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take FOSAMAX. Take calcium and vitamin D as your doctor tells you to.

3. **Bone, joint, or muscle pain.**
   Some people who take FOSAMAX develop severe bone, joint, or muscle pain.

4. **Severe jaw bone problems (osteonecrosis).**
   Severe jaw bone problems may happen when you take FOSAMAX. Your doctor should examine your mouth before you start FOSAMAX. Your doctor may tell you to see your dentist before you start FOSAMAX. It is important for you to practice good mouth care during treatment with FOSAMAX.

5. **Unusual thigh bone fractures.**
   Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is FOSAMAX?

FOSAMAX is a prescription medicine used to:

- Treat or prevent osteoporosis in women after menopause. It helps reduce the chance of having a hip or spinal fracture (break).
- Increase bone mass in men with osteoporosis.
- Treat osteoporosis in either men or women who are taking corticosteroid medicines.
- Treat certain men and women who have Paget's disease of the bone.

It is not known how long FOSAMAX works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if FOSAMAX is still right for you.

FOSAMAX is not for use in children.

Who should not take FOSAMAX?

Do not take FOSAMAX if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to FOSAMAX or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking FOSAMAX?

Before you start FOSAMAX, be sure to talk to your doctor if you:

- Have problems with swallowing
- Have stomach or digestive problems
- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant, or plan to become pregnant. It is not known if FOSAMAX can harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if FOSAMAX passes into your milk and may harm your baby.

Especially tell your doctor if you take:

- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how FOSAMAX works.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take FOSAMAX?

- Take FOSAMAX exactly as your doctor tells you.
- **FOSAMAX works only if taken on an empty stomach.**
- Take FOSAMAX, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take FOSAMAX while you are sitting or standing.
- **Do not chew or suck on a tablet of FOSAMAX.**
- Swallow FOSAMAX tablet with a full glass (6-8 oz) of plain water only.
- **Do not** take FOSAMAX with mineral water, coffee, tea, soda, or juice.

  - If you take **FOSAMAX Daily**:
    - Take 1 FOSAMAX tablet one time a day, every day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
  - If you take **Once Weekly FOSAMAX**:
    - Choose the day of the week that best fits your schedule.
    - Take 1 dose of FOSAMAX every week on your chosen day **after** you get up for the day and **before** taking your first food, drink, or other medicine.
  - If you take **FOSAMAX Oral Solution**:
    - Drink your prescribed dose of FOSAMAX Oral Solution every week on your chosen day **after** you get up for the day and **before** taking your first food, drink or other medicine. Drink at least 2 ounces of plain water after you drink FOSAMAX Oral Solution.

After swallowing FOSAMAX tablet or oral solution, wait at least 30 minutes:

- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take your first food or drink except for plain water.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take FOSAMAX and after you eat your first food of the day.

If you miss a dose of FOSAMAX, do not take it later in the day. Take your missed dose on the next morning after you remember and then return to your normal schedule. Do not take 2 doses on the same day.

If you take too much FOSAMAX, call your doctor. Do not try to vomit. Do not lie down.

What are the possible side effects of FOSAMAX?

FOSAMAX may cause serious side effects.

- See **"What is the most important information I should know about FOSAMAX?"**

The most common side effects of FOSAMAX are:

- Stomach area (abdominal) pain
- Heartburn
- Constipation
- Diarrhea
- Upset stomach
- Pain in your bones, joints, or muscles
- Nausea

You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or

throat.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of FOSAMAX. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store FOSAMAX?

- Store FOSAMAX at room temperature, 59°F to 86°F (15°C to 30°C).
- Keep FOSAMAX in a tightly closed container.

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

General information about the safe and effective use of FOSAMAX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FOSAMAX for a condition for which it was not prescribed. Do not give FOSAMAX to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about FOSAMAX. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about FOSAMAX that is written for health professionals.

For more information, go to: www.FOSAMAX.com or call 1-877-408-4699.

What are the ingredients in FOSAMAX?
Tablets:
Active ingredient: alendronate sodium
Inactive ingredients: cellulose, lactose, croscarmellose sodium, magnesium stearate.
In addition the 10 mg tablet also contains carnauba wax.

Oral Solution:
Active ingredient: alendronate monosodium salt trihydrate
Inactive ingredients: sodium citrate dihydrate, citric acid anhydrous, sodium saccharin, artificial raspberry flavor, water, sodium propylparaben 0.0225%, sodium butylparaben 0.0075%.

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Whitehouse Station, NJ 08889, USA

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FOSAMAX PLUS D safely and effectively. See full prescribing information for FOSAMAX PLUS D.

FOSAMAX® PLUS D
(alendronate sodium/cholecalciferol) tablets
Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Indications and Usage, Limitations of Use (1.3)	01/2011
Warnings and Precautions, Femoral Fractures (5.5)	01/2011

INDICATIONS AND USAGE

FOSAMAX PLUS D is a combination of a bisphosphonate and vitamin D indicated for:

- Treatment of osteoporosis in postmenopausal women (1.1)
- Treatment to increase bone mass in men with osteoporosis (1.2)

FOSAMAX PLUS D alone should not be used to treat vitamin D deficiency. (1.3)
The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

DOSAGE AND ADMINISTRATION

Must be taken with plain water (6 to 8 oz) at least 30 minutes before the first food or drink of the day; do not lie down for 30 minutes. (2.3)

- 70 mg alendronate/2800 IU vitamin D_3 or 70 mg alendronate/5600 IU vitamin D_3 tablet once weekly. (2.1, 2.2, 2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: 70 mg/2800 IU and 70 mg/5600 IU (3)

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay emptying such as stricture or achalasia (4, 5.1)
- Inability to stand/sit upright for at least 30 minutes (4, 5.1)
- Hypocalcemia (4, 5.2)
- Hypersensitivity to any component of this product (4, 6.2)

WARNINGS AND PRECAUTIONS

- Severe irritation of upper gastrointestinal mucosa can occur. Follow dosing instructions. Use caution in patients with active upper GI disease. Discontinue if new or worsening symptoms occur. (5.1)
- Hypocalcemia can worsen and must be corrected prior to use. (5.2)
- Severe bone, joint, muscle pain may occur. Discontinue use if severe symptoms develop. (5.3)
- Osteonecrosis of the jaw has been reported rarely. (5.4)
- Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out an incomplete femoral fracture. (5.5)

ADVERSE REACTIONS

The most common adverse reactions for alendronate (incidence ≥3%) are: abdominal pain, acid regurgitation, constipation, diarrhea, dyspepsia, musculoskeletal pain, nausea. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Calcium supplements/antacids and some medications will likely interfere with absorption of alendronate and should be taken at least 30 minutes after FOSAMAX PLUS D. (2.3, 7.1)
- Aspirin and nonsteroidal anti-inflammatory drug use may worsen gastrointestinal irritation; caution should be used. (7.2, 7.3)
- Some drugs may impair the absorption or increase the catabolism of cholecalciferol (vitamin D_3). Additional vitamin D supplementation should be considered. (7.4, 7.5, 12.3)

USE IN SPECIFIC POPULATIONS

- FOSAMAX PLUS D is not indicated for use in children. (8.4)
- FOSAMAX PLUS D is not recommended in patients with severe renal insufficiency (creatinine clearance <35 mL/min). (2.5, 5.6)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 03/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FOSAMAX® PLUS D is indicated for:

1.1 Treatment of Osteoporosis in Postmenopausal Women

For the treatment of osteoporosis, FOSAMAX PLUS D increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures).

1.2 Treatment to Increase Bone Mass in Men with Osteoporosis

1.3 Important Limitations of Use

FOSAMAX PLUS D alone should not be used to treat vitamin D deficiency.

The safety and effectiveness of FOSAMAX PLUS D for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of Osteoporosis in Postmenopausal Women

The recommended dosage is one 70 mg alendronate/2800 IU vitamin D_3 or one 70 mg alendronate/5600 IU vitamin D_3 tablet once weekly. For most osteoporotic women, the appropriate dose is FOSAMAX PLUS D (70 mg alendronate/5600 IU vitamin D_3) once weekly.

2.2 Treatment to Increase Bone Mass in Men with Osteoporosis

The recommended dosage is one 70 mg alendronate/2800 IU vitamin D_3 or one 70 mg alendronate/5600 IU vitamin D_3 tablet once weekly. For most osteoporotic men, the appropriate dose is FOSAMAX PLUS D (70 mg alendronate/5600 IU vitamin D_3) once weekly.

2.3 Dosing Instructions

FOSAMAX PLUS D must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only *[see Medication Guide]*. Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate *[see Drug Interactions (7.1)]*. Waiting less than 30 minutes, or taking FOSAMAX PLUS D with food, beverages (other than plain water) or other medications will lessen the effect of alendronate by decreasing its absorption into the body.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FOSAMAX® PLUS D is indicated for:

1.1 Treatment of Osteoporosis in Postmenopausal Women

For the treatment of osteoporosis, FOSAMAX PLUS D increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures).

1.2 Treatment to Increase Bone Mass in Men with Osteoporosis

1.3 Important Limitations of Use

FOSAMAX PLUS D alone should not be used to treat vitamin D deficiency.

The safety and effectiveness of FOSAMAX PLUS D for the treatment of osteoporosis are based on clinical data of four years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of Osteoporosis in Postmenopausal Women

The recommended dosage is one 70 mg alendronate/2800 IU vitamin D_3 or one 70 mg alendronate/5600 IU vitamin D_3 tablet once weekly. For most osteoporotic women, the appropriate dose is FOSAMAX PLUS D (70 mg alendronate/5600 IU vitamin D_3) once weekly.

2.2 Treatment to Increase Bone Mass in Men with Osteoporosis

The recommended dosage is one 70 mg alendronate/2800 IU vitamin D_3 or one 70 mg alendronate/5600 IU vitamin D_3 tablet once weekly. For most osteoporotic men, the appropriate dose is FOSAMAX PLUS D (70 mg alendronate/5600 IU vitamin D_3) once weekly.

2.3 Dosing Instructions

FOSAMAX PLUS D must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only *[see Medication Guide]*. Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of alendronate *[see Drug Interactions (7.1)]*. Waiting less than 30 minutes, or taking FOSAMAX PLUS D with food, beverages (other than plain water) or other medications will lessen the effect of alendronate by decreasing its absorption into the body.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX PLUS D *[see Contraindications (4)]*. Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX PLUS D.
Presumably due to the effects of alendronate on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur.
Cholecalciferol
FOSAMAX PLUS D alone should not be used to treat vitamin D deficiency (commonly defined as 25-hydroxyvitamin D level below 9 ng/mL). Patients at increased risk for vitamin D insufficiency may require higher doses of vitamin D supplementation *[see Dosage and Administration (2.4)]*. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.
Vitamin D_3 supplementation may worsen hypercalcemia and/or hypercalciuria when administered to patients with diseases associated with unregulated overproduction of 1,25 dihydroxyvitamin D (e.g., leukemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.

5.3 Musculoskeletal Pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis *[see Adverse Reactions (6.2)]*. This category of drugs includes alendronate. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.
In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

5.4 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including FOSAMAX PLUS D. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).
For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.
Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.6 Renal Insufficiency
FOSAMAX PLUS D is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). *[See Dosage and Administration (2.5).]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
FOSAMAX

FOSAMAX has been evaluated for safety in approximately 8000 postmenopausal women in clinical studies.

Postmenopausal Women

FOSAMAX daily

In two identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational; n=994), discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX 10 mg/day and 6.0% of 397 patients treated with placebo. In the Fracture Intervention Trial (n=6459), discontinuation of therapy due to any clinical adverse experience occurred in 9.1% of 3236 patients treated with FOSAMAX 5 mg/day for 2 years and 10 mg/day for either one or two additional years and 10.1% of 3223 patients treated with placebo. Discontinuations due to upper gastrointestinal adverse experiences were: FOSAMAX, 3.2%; placebo, 2.7%. In these study populations, 49-54% had a history of gastrointestinal disorders at baseline and 54-89% used nonsteroidal anti-inflammatory drugs or aspirin at some time during the studies. Adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX or placebo are presented in Table 1.

Table 1: Osteoporosis Treatment Studies in Postmenopausal Women: Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	United States/Multinational Studies		Fracture Intervention Trial	
	FOSAMAX* % (n=196)	Placebo % (n=397)	FOSAMAX† % (n=3236)	Placebo % (n=3223)
Gastrointestinal	6.6	4.8	1.5	1.5
abdominal pain	3.6	4.0	1.1	1.5
nausea	3.6	3.5	1.1	1.2
dyspepsia	3.1	1.8	0.0	0.2
constipation	3.1	1.8	0.6	0.3
diarrhea	2.6	0.5	0.2	0.3
flatulence	2.0	4.3	1.1	0.9
acid regurgitation	1.5	0.0	0.1	0.1
esophageal ulcer	1.0	1.5	0.2	0.3
vomiting	1.0	0.0	0.1	0.1
dysphagia	1.0	0.8	0.0	0.0
abdominal distention	0.5	1.3	0.6	0.7
gastritis				
Musculoskeletal	4.1	2.5	0.4	0.3
musculoskeletal (bone, muscle or joint) pain	0.0	1.0	0.2	0.1
muscle cramp				
Nervous System/Psychiatric	2.6	1.5	0.2	0.2
headache	0.0	1.0	0.0	0.1
dizziness				
Special Senses	0.5	1.0	0.1	0.0
taste perversion				

*10 mg/day for three years

†5 mg/day for 2 years and 10 mg/day for either 1 or 2 additional years

Rarely, rash and erythema have occurred.

The adverse experience profile was similar for the 401 patients treated with either 5- or 20-mg doses of FOSAMAX in the United States and Multinational studies. The adverse experience profile for the 296 patients who received continued treatment with either 5- or 10-mg doses of FOSAMAX in the two-year extension of these studies (treatment years 4 and 5) was similar to that observed during the three-year placebo-controlled period. During the extension period, of the 151 patients treated with FOSAMAX 10 mg/day, the proportion of patients who discontinued therapy due to any clinical adverse experience was similar to that during the first three years of the study.

FOSAMAX Once-Weekly

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 70 mg and FOSAMAX 10 mg daily were similar. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients in either treatment group are presented in Table 2.

Table 2: Osteoporosis Treatment Studies in Postmenopausal Women: Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients

	Once Weekly FOSAMAX 70 mg % (n=519)	FOSAMAX 10 mg/day % (n=370)
Gastrointestinal	3.7	3.0
abdominal pain	2.7	2.2
dyspepsia	1.9	2.4
acid regurgitation	1.9	2.4
nausea	1.0	1.4
abdominal distention	0.8	1.6
constipation	0.4	1.6
flatulence	0.2	1.1
gastritis	0.0	1.1
gastric ulcer		
Musculoskeletal	2.9	3.2
musculoskeletal (bone, muscle, joint) pain	0.2	1.1
muscle cramp		

Concomitant Use With Estrogen or Estrogen/Progestin Products

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Men

In two placebo-controlled, double-blind, multicenter studies in men (a two-year study of FOSAMAX 10 mg/day and a one-year study of once weekly FOSAMAX 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in Table 3.

Table 3: Osteoporosis Studies in Men: Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients

	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=109)	Placebo % (n=58)
Gastrointestinal	4.1	3.2	0.0	0.0
acid regurgitation	4.1	1.1	0.0	0.0
flatulence	0.7	3.2	2.8	0.0
gastroesophageal reflux disease	3.4	0.0	2.8	1.7
dyspepsia	1.4	1.1	2.8	0.0
diarrhea	2.1	1.1	0.9	3.4
abdominal pain	2.1	0.0	0.0	0.0
nausea				

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to ≤2.0 mg/dL (0.65 mM) were similar in both treatment groups.

FOSAMAX PLUS D

In a fifteen-week double-blind, multinational study in osteoporotic postmenopausal women (n=682) and men (n=35), the safety profile of FOSAMAX PLUS D (70 mg/2800 IU) was similar to that of FOSAMAX once weekly 70 mg. In the 24-week double-blind extension study in women (n=619) and men (n=33), the safety profile of FOSAMAX PLUS D (70 mg/2800 IU) administered with an additional 2800 IU vitamin D_3 was similar to that of FOSAMAX PLUS D (70 mg/2800 IU).

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of FOSAMAX and FOSAMAX PLUS D. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise, asthenia and rarely, fever have been reported with alendronate, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions. Rarely, peripheral edema.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported *[see Dosage and Administration (2.3); Warnings and Precautions (5.1); Medication Guide]*.

Localized osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection with delayed healing, has been reported rarely *[see Warnings and Precautions (5.4)]*.

Musculoskeletal: bone, joint, and/or muscle pain, occasionally severe, and rarely incapacitating *[see Warnings and Precautions (5.3)]*; joint swelling; low-energy femoral shaft and subtrochanteric fractures *[see Warnings and Precautions (5.5)]*.

Nervous System: dizziness and vertigo.

Skin: rash (occasionally with photosensitivity), pruritus, alopecia, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, scleritis or episcleritis.

7 DRUG INTERACTIONS

7.1 Calcium Supplements/Antacids

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of alendronate. Therefore, patients must wait at least one-half hour after taking FOSAMAX PLUS D before taking any other oral medications.

7.2 Aspirin

In clinical studies, the incidence of upper gastrointestinal adverse events was increased in patients receiving concomitant therapy with daily doses of FOSAMAX greater than 10 mg and aspirin-containing products.

7.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

FOSAMAX PLUS D may be administered to patients taking NSAIDs. In a 3-year, controlled, clinical study (n=2027) during which a majority of patients received concomitant NSAIDs, the incidence of upper gastrointestinal adverse events was similar in patients taking FOSAMAX 5 or 10 mg/day compared to those taking placebo. However, since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with FOSAMAX PLUS D.

7.4 Drugs that May Impair the Absorption of Cholecalciferol

Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g., cholestyramine, colestipol) may impair the absorption of vitamin D. Additional vitamin D supplementation should be considered *[see Clinical Pharmacology (12.3)]*.

7.5 Drugs that May Increase the Catabolism of Cholecalciferol

Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D. Additional vitamin D supplementation should be considered *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

Alendronate Sodium

Reproduction studies in rats showed decreased postimplantation survival at 2 mg/kg/day and decreased body weight gain in normal pups at 1 mg/kg/day. Sites of incomplete fetal ossification were statistically significantly increased in rats beginning at 10 mg/kg/day in vertebral (cervical, thoracic, and lumbar), skull, and sternebral bones. The above doses ranged from one time (1 mg/kg) to 10 times (10 mg/kg) a maximum recommended daily dose of 10 mg/day based on surface area, mg/m^2. No similar fetal effects were seen when pregnant rabbits were treated at doses up to 35 mg/kg/day (40 times a 10 mg human daily dose based on surface area, mg/m^2).

Both total and ionized calcium decreased in pregnant rats at 15 mg/kg/day (13 times a 10-mg human daily dose based on surface area, mg/m^2) resulting in delays and failures of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 0.5 mg/kg/day (0.5 times a 10 mg human daily dose based on surface area, mg/m^2) when rats were treated from before mating through gestation. Maternotoxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were lessened but not eliminated by cessation of treatment. Calcium supplementation either in the drinking water or by minipump could not

ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.
Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.
Cholecalciferol
No data are available for cholecalciferol (vitamin D_3). Administration of high doses (≥10,000 IU/every other day) of ergocalciferol (vitamin D_2) to pregnant rabbits resulted in abortions and an increased incidence of fetal aortic stenosis. Administration of vitamin D_2 (40,000 IU/day) to pregnant rats resulted in neonatal death, decreased fetal weight, and impaired osteogenesis of long bones postnatally.
There are no studies in pregnant women. FOSAMAX PLUS D should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

8.3 Nursing Mothers
Cholecalciferol and some of its active metabolites pass into breast milk. It is not known whether alendronate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSAMAX PLUS D is administered to nursing women.

8.4 Pediatric Use
FOSAMAX PLUS D is not indicated for use in children.
The efficacy and safety of alendronate were examined in a randomized, double-blind, placebo-controlled two-year study of 139 pediatric patients, aged 4-18 years, with severe osteogenesis imperfecta. One-hundred-and-nine patients were randomized to 5 mg alendronate daily (weight <40 kg) or 10 mg alendronate daily (weight ≥40 kg) and 30 patients to placebo. The mean baseline lumbar spine BMD Z-score of the patients was -4.5. The mean change in lumbar spine BMD Z-score from baseline to Month 24 was 1.3 in the alendronate-treated patients and 0.1 in the placebo-treated patients. Treatment with alendronate did not reduce the risk of fracture. Sixteen percent of the alendronate patients who sustained a radiologically-confirmed fracture by Month 12 of the study had delayed fracture healing (callus remodeling) or fracture non-union when assessed radiographically at Month 24 compared with 9% of the placebo-treated patients. In alendronate-treated patients, bone histomorphometry data obtained at Month 24 demonstrated decreased bone turnover and delayed mineralization time; however, there were no mineralization defects. There were no statistically significant differences between the alendronate and placebo groups in reduction of bone pain.

8.5 Geriatric Use
Of the patients receiving FOSAMAX in the Fracture Intervention Trial (FIT), 71% (n=2302) were ≥65 years of age and 17% (n=550) were ≥75 years of age. Of the patients receiving FOSAMAX in the United States and Multinational osteoporosis treatment studies in women, and osteoporosis studies in men *[see Clinical Studies (14.1, 14.2)]*, 45% and 54%, respectively, were 65 years of age or over. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dietary requirements of vitamin D_3 are increased in the elderly.

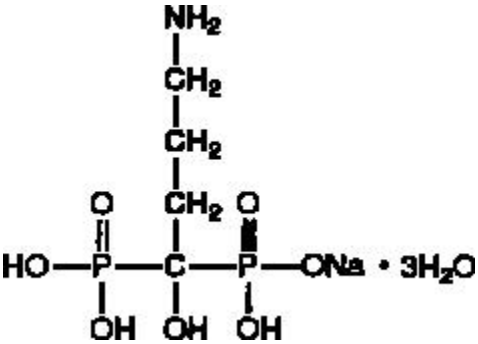
10 OVERDOSAGE
Alendronate Sodium
Significant lethality after single oral doses with alendronate was seen in female rats and mice at 552 mg/kg (3256 mg/m^2) and 966 mg/kg (2898 mg/m^2), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 200 mg/kg (4000 mg/m^2).
No specific information is available on the treatment of overdosage with alendronate. Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.
Dialysis would not be beneficial.
Cholecalciferol
Significant lethality occurred in mice treated with a single high oral dose of calcitriol (4 mg/kg), the hormonal metabolite of cholecalciferol.
There is limited information regarding doses of cholecalciferol associated with acute toxicity, although intermittent (yearly or twice yearly) single doses of ergocalciferol (vitamin D_2) as high as 600,000 IU have been given without reports of toxicity. Signs and symptoms of vitamin D toxicity include hypercalcemia, hypercalciuria, anorexia, nausea, vomiting, polyuria, polydipsia, weakness,

and lethargy. Serum and urine calcium levels should be monitored in patients with suspected vitamin D toxicity. Standard therapy includes restriction of dietary calcium, hydration, and systemic glucocorticoids in patients with severe hypercalcemia.
Dialysis to remove vitamin D would not be beneficial.

11 DESCRIPTION

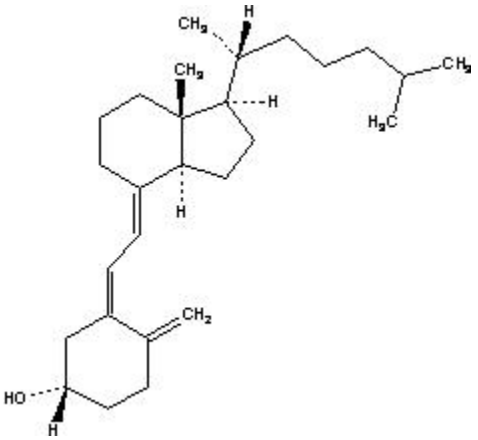
FOSAMAX PLUS D contains alendronate sodium, a bisphosphonate, and cholecalciferol (vitamin D_3).

Alendronate sodium is a bisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.
Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate.
The empirical formula of alendronate sodium is $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ and its formula weight is 325.12. The structural formula is:



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.
Cholecalciferol (vitamin D_3) is a secosterol that is the natural precursor of the calcium-regulating hormone calcitriol (1,25 dihydroxyvitamin D_3).

The chemical name of cholecalciferol is (3β,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3-ol. The empirical formula of cholecalciferol is $C_{27}H_{44}O$ and its molecular weight is 384.6. The structural formula is:



Cholecalciferol is a white, crystalline, odorless powder. Cholecalciferol is practically insoluble in water, freely soluble in usual organic solvents, and slightly soluble in vegetable oils.
FOSAMAX PLUS D for oral administration contains 91.37 mg of alendronate monosodium salt trihydrate, the molar equivalent of 70 mg of free acid, and 70 or 140 mcg of cholecalciferol, equivalent to 2800 or 5600 International Units (IU) vitamin D, respectively.
Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alendronate Sodium

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10–fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While

incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Cholecalciferol

Vitamin D_3 is produced in the skin by photochemical conversion of 7-dehydrocholesterol to previtamin D_3 by ultraviolet light. This is followed by non-enzymatic isomerization to vitamin D_3. In the absence of adequate sunlight exposure, vitamin D_3 is an essential dietary nutrient. Vitamin D_3 in skin and dietary vitamin D_3 (absorbed into chylomicrons) is converted to 25–hydroxyvitamin D_3 in the liver. Conversion to the active calcium-mobilizing hormone 1,25-dihydroxyvitamin D_3 (calcitriol) in the kidney is stimulated by both parathyroid hormone and hypophosphatemia. The principal action of 1,25–dihydroxyvitamin D_3 is to increase intestinal absorption of both calcium and phosphate as well as regulate serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption.

Vitamin D is required for normal bone formation. Vitamin D insufficiency develops when both sunlight exposure and dietary intake are inadequate. Insufficiency is associated with negative calcium balance, increased parathyroid hormone levels, bone loss, and increased risk of skeletal fracture. In severe cases, deficiency results in more severe hyperparathyroidism, hypophosphatemia, proximal muscle weakness, bone pain and osteomalacia.

12.2 Pharmacodynamics

Alendronate Sodium

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N–telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N–telopeptides of type l collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau after 6 to 12 months. Similar reductions in the rate of bone turnover were observed in postmenopausal women during one-year studies with once weekly FOSAMAX 70 mg for the treatment of osteoporosis. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX 10 mg. No further decreases in serum calcium were observed for the five-year duration of treatment; however, serum phosphate returned toward prestudy levels during years three through five. In one-year studies with once weekly FOSAMAX 70 mg, similar reductions were observed at 6 and 12 months. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX but also a decrease in renal phosphate reabsorption.

Osteoporosis in Men

Treatment of men with osteoporosis with FOSAMAX 10 mg/day for two years reduced urinary excretion of cross-linked N-telopeptides of type I collagen by approximately 60% and bone-specific alkaline phosphatase by approximately 40%. Similar reductions were observed in a one-year study in men with osteoporosis receiving once weekly FOSAMAX 70 mg.

Cholecalciferol

Vitamin D is required for normal bone formation. Vitamin D insufficiency is associated with negative calcium balance, leading to increased parathyroid hormone levels and worsening of bone loss associated with osteoporosis. When taken without vitamin D, alendronate is also associated with a reduction in serum calcium concentrations and increased parathyroid hormone levels. In a 15–week trial, 717 postmenopausal women and men, mean age 67 years, with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2.5 standard deviations below the premenopausal mean) were randomized to receive either weekly FOSAMAX PLUS D 70 mg/2800 IU vitamin D or weekly FOSAMAX 70 mg alone with no vitamin D supplementation. Patients who were vitamin D deficient (25–hydroxyvitamin D <9 ng/mL) at baseline were excluded. Treatment with FOSAMAX PLUS D 70 mg/2800 IU resulted in a smaller reduction in serum calcium levels (-0.9%) when compared to FOSAMAX 70 mg alone (-1.4%). As well, treatment with FOSAMAX PLUS D 70 mg/2800 IU resulted in a significantly smaller increase in parathyroid hormone levels when compared to FOSAMAX 70 mg alone (14% and 24%, respectively).

The sufficiency of patients' vitamin D status is best assessed by measuring 25-hydroxyvitamin D levels. In the 15–week trial mentioned above, baseline 25-hydroxyvitamin D levels were 22.2 ng/mL in the FOSAMAX PLUS D group and 22.1 ng/mL in the FOSAMAX only group. After 15 weeks of treatment, the mean levels were 23.1 ng/mL and 18.4 ng/mL in the FOSAMAX PLUS D and FOSAMAX only groups, respectively. The final levels of 25-hydroxyvitamin D at Week 15 are summarized in Table 4.

Table 4: 25-hydroxyvitamin D Levels after Treatment with FOSAMAX PLUS D (70 mg/2800 IU) or FOSAMAX 70 mg at Week 15*

	Number (%) of Patients					
25-hydroxyvitamin D Ranges (ng/mL)	**<9**	**9-14**	**15-19**	**20-24**	**25-29**	**30-62**
FOSAMAX PLUS D (70 mg/2800 IU) (N=357)	4 (1.1)	37 (10.4)	87 (24.4)	84 (23.5)	82 (23.0)	63 (17.7)
FOSAMAX 70 mg (N=351)	46 (13.1)	66 (18.8)	108 (30.8)	58 (16.5)	37 (10.5)	36 (10.3)

*****Patients who were vitamin D deficient (25-hydroxyvitamin D <9 ng/mL) at baseline were excluded.

Patients (n=652) who completed the above 15-week trial continued in a 24-week extension in which all received FOSAMAX PLUS D (70 mg/2800 IU) and were randomly assigned to receive either additional once weekly vitamin D_3 2800 IU (Vitamin D_3 5600 IU group) or matching placebo (Vitamin D_3 2800 IU group). After 24 weeks of extended treatment (Week 39 from original baseline), the mean levels of 25-hydroxyvitamin D were 27.9 ng/mL and 25.6 ng/mL in the vitamin D_3 5600 IU group and vitamin D_3 2800 IU group, respectively. The percentage of patients with hypercalciuria at Week 39 was not statistically different between treatment groups.

The distribution of the final levels of 25-hydroxyvitamin D at Week 39 is summarized in Table 5.

Table 5: 25-hydroxyvitamin D Levels after Treatment with FOSAMAX PLUS D at Week 39

	Number (%) of Patients					
25-hydroxyvitamin D Ranges (ng/mL)	**<9**	**9-14**	**15-19**	**20-24**	**25-29**	**30-59**
FOSAMAX PLUS D (Vitamin D_3 5600 IU group)* (N=321)	0	10 (3.1)	29 (9.0)	79 (24.6)	87 (27.1)	116 (36.1)
FOSAMAX PLUS D (Vitamin D_3 2800 IU group)† (N=320)	1 (0.3)	17 (5.3)	56 (17.5)	80 (25.0)	74 (23.1)	92 (28.8)

*****Patients received FOSAMAX 70 mg or FOSAMAX PLUS D (70 mg/2800 IU) for the 15-week base study followed by FOSAMAX PLUS D (70 mg/2800 IU) and 2800 IU additional vitamin D_3 for the 24-week extension study.

†Patients received FOSAMAX 70 mg or FOSAMAX PLUS D (70 mg/2800 IU) for 15-week base study followed by FOSAMAX PLUS D (70 mg/2800 IU) and placebo for the additional vitamin D_3 for 24-week extension study.

12.3 Pharmacokinetics

Absorption

Alendronate Sodium

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10-mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

In a study, the alendronate in the FOSAMAX PLUS D (70 mg/2800 IU) tablet and the FOSAMAX (alendronate sodium) 70-mg tablet were found to be equally bioavailable. In a separate study, the alendronate in the FOSAMAX PLUS D (70 mg/5600 IU) tablet was found to be equally bioavailable to the alendronate in the FOSAMAX (alendronate sodium) 70-mg tablet.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Cholecalciferol

Following administration of FOSAMAX PLUS D (70 mg/2800 IU) after an overnight fast and two hours before a standard meal, the baseline adjusted mean area under the serum-concentration-time curve ($AUC_{0\text{-}120\ hrs}$) for vitamin D_3 was 120.7 ng-hr/mL. The baseline adjusted mean maximal serum concentration (C_{max}) of vitamin D_3 was 4.0 ng/mL, and the baseline adjusted mean time to maximal serum concentration (T_{max}) was 10.6 hrs. The bioavailability of the 2800 IU vitamin D_3 in FOSAMAX PLUS D is similar to 2800 IU vitamin D_3 administered alone.

In a separate study, the baseline adjusted mean $AUC_{0\text{-}80\ hrs}$ and baseline adjusted mean C_{max} for vitamin D_3 were 355.6 ng-hr/mL and 10.8 ng/mL, respectively. The baseline adjusted mean T_{max} was 9.2 hrs. The bioavailability of the 5600 IU vitamin D_3 in the FOSAMAX PLUS D is similar to 5600 IU vitamin D_3 administered as two 2800 IU vitamin D_3 tablets.

Distribution

Alendronate Sodium

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Cholecalciferol

Following absorption, vitamin D_3 enters the blood as part of chylomicrons. Vitamin D_3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D_3, the major storage form. Lesser amounts are distributed to adipose tissue and stored as vitamin D_3 at these sites for later release into the circulation. Circulating vitamin D_3 is bound to vitamin D-binding protein.

Metabolism

Alendronate Sodium

There is no evidence that alendronate is metabolized in animals or humans.

Cholecalciferol

Vitamin D_3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D_3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D_3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination.

Excretion

Alendronate Sodium

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10-mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Cholecalciferol

When radioactive vitamin D_3 was intravenously administered to healthy subjects, the mean urinary excretion of radioactivity after 48 hours was 2.4% of the administered dose, and the mean fecal excretion of radioactivity after 48 hours was 4.9% of the administered dose. In both cases, the excreted radioactivity was almost exclusively as metabolites of the parent. The mean half-life of baseline adjusted vitamin D_3 in the serum following an oral dose of FOSAMAX PLUS D is approximately 14 hours.

Special Populations

Pediatric: The oral bioavailability of alendronate in children was similar to that observed in adults; however, FOSAMAX PLUS D is not indicated for use in children *[see Use in Specific Populations (8.4)]*.

Gender: Bioavailability and the fraction of an IV dose of alendronate excreted in urine were similar in men and women.

Geriatric:

Alendronate Sodium

Bioavailability and disposition of alendronate (urinary excretion) were similar in elderly and younger patients. No dosage adjustment of alendronate is necessary *[see Dosage and Administration (2.5)]*.

Cholecalciferol

Dietary requirements of vitamin D_3 are increased in the elderly.

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency:

Alendronate Sodium

Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX PLUS D is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.

Cholecalciferol

Patients with renal insufficiency will have decreased ability to form the active 1,25-dihydroxyvitamin D_3 metabolite.

Hepatic Insufficiency:

Alendronate Sodium
As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.
Cholecalciferol
Vitamin D_3 may not be adequately absorbed in patients who have malabsorption due to inadequate bile production.
Drug Interactions
Alendronate Sodium
Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.
In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).
Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.
Cholecalciferol
Olestra, mineral oils, orlistat, and bile acid sequestrants (e.g., cholestyramine, colestipol) may impair the absorption of vitamin D.
Anticonvulsants, cimetidine, and thiazides may increase the catabolism of vitamin D.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
The following data are based on findings for the individual components of FOSAMAX PLUS D.
Alendronate Sodium
Harderian gland (a retro-orbital gland not present in humans) adenomas were increased in high-dose female mice (p=0.003) in a 92–week oral carcinogenicity study at doses of alendronate of 1, 3, and 10 mg/kg/day (males) or 1, 2, and 5 mg/kg/day (females). These doses are equivalent to 0.5 to 4 times a maximum recommended daily dose of 10 mg based on surface area, mg/m^2. The relevance of this finding to humans is unknown.
Parafollicular cell (thyroid) adenomas were increased in high-dose male rats (p=0.003) in a 2–year oral carcinogenicity study at doses of 1 and 3.75 mg/kg body weight. These doses are equivalent to 1 and 4 times a 10-mg human daily dose based on surface area, mg/m^2. The relevance of this finding to humans is unknown.
Alendronate was not genotoxic in the *in vitro* microbial mutagenesis assay with and without metabolic activation, in an *in vitro* mammalian cell mutagenesis assay, in an *in vitro* alkaline elution assay in rat hepatocytes, and in an *in vivo* chromosomal aberration assay in mice. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, however, alendronate gave equivocal results.
Alendronate had no effect on fertility (male or female) in rats at oral doses up to 5 mg/kg/day (4 times a 10-mg human daily dose based on surface area, mg/m^2).
Cholecalciferol
The carcinogenic potential of cholecalciferol (vitamin D_3) has not been studied in rodents. Calcitriol, the hormonal metabolite of cholecalciferol, was not genotoxic in the Ames microbial mutagenesis assay with or without metabolic activation, and in an *in vivo* micronucleus assay in mice.
Ergocalciferol (vitamin D_2) at high doses (150,000 to 200,000 IU/kg/day) administered prior to mating resulted in altered estrous cycle and inhibition of pregnancy in rats. The potential effect of cholecalciferol on male fertility is unknown in rats.

13.2 Animal Toxicology and/or Pharmacology
The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000–fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.

14 CLINICAL STUDIES

14.1 Treatment of Postmenopausal Osteoporosis
Effect on Fracture Incidence
Data on the effects of FOSAMAX on fracture incidence are derived from three clinical studies of postmenopausal women, 44 to 84 years of age, with osteoporosis: 1) U.S. and Multinational combined: a study of patients with a lumbar spine BMD T-score at or below minus 2.5 with or without a prior vertebral fracture, 2) Three-Year Study of the Fracture Intervention Trial (FIT): a study of patients with at least one baseline vertebral fracture, and 3) Four-Year Study of FIT: a study of patients with low bone mass but without a baseline vertebral fracture.
To assess the effects of FOSAMAX on the incidence of vertebral fractures (detected by digitized radiography; approximately one third of these were clinically symptomatic), the U.S. (478 patients) and Multinational (516 patients in 15 countries) studies (of virtually

identical design) were combined in an analysis that compared placebo to the pooled dosage groups of FOSAMAX (5 or 10 mg for three years or 20 mg for two years followed by 5 mg for one year). There was a statistically significant reduction in the proportion of patients treated with FOSAMAX experiencing one or more new vertebral fractures relative to those treated with placebo (3.2% vs. 6.2%; a 48% relative risk reduction). A reduction in the total number of new vertebral fractures (4.2 vs. 11.3 per 100 patients) was also observed. In the pooled analysis, patients who received FOSAMAX had a loss in stature that was statistically significantly less than was observed in those who received placebo (-3.0 mm vs. -4.6 mm).

The Fracture Intervention Trial (FIT) consisted of two studies in postmenopausal women: the Three-Year Study of patients who had at least one baseline radiographic vertebral fracture and the Four-Year Study of patients with low bone mass but without a baseline vertebral fracture. In both studies of FIT, 96% of randomized patients completed the studies (i.e., had a closeout visit at the scheduled end of the study); approximately 80% of patients were still taking study medication upon completion.

Fracture Intervention Trial: Three-Year Study (patients with at least one baseline radiographic vertebral fracture)

This randomized, double-blind, placebo-controlled, 2027-patient study (FOSAMAX, n=1022; placebo, n=1005) demonstrated that treatment with FOSAMAX resulted in statistically significant reductions in fracture incidence at three years as shown in Table 6.

Table 6: Effect of FOSAMAX on Fracture Incidence in the Three-Year Study of FIT (patients with vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1022)	Placebo (n=1005)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk %
Patients with:				
Vertebral fractures (diagnosed by X-ray)*				
≥1 new vertebral fracture	7.9	15.0	7.1	47†
≥2 new vertebral fractures	0.5	4.9	4.4	90†
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	13.8	18.1	4.3	26‡
≥1 clinical (symptomatic) vertebral fracture	2.3	5.0	2.7	54§
Hip fracture	1.1	2.2	1.1	51¶
Wrist (forearm) fracture	2.2	4.1	1.9	48¶

*Number evaluable for vertebral fractures: FOSAMAX, n=984; placebo, n=966
†p<0.001
‡p=0.007
§p<0.01
¶p<0.05

Furthermore, in this population of patients with baseline vertebral fracture, treatment with FOSAMAX significantly reduced the incidence of hospitalizations (25.0% vs. 30.7%).

In the Three-Year Study of FIT, fractures of the hip occurred in 22 (2.2%) of 1005 patients on placebo and 11 (1.1%) of 1022 patients on FOSAMAX, p=0.047. Figure 1 displays the cumulative incidence of hip fractures in this study.

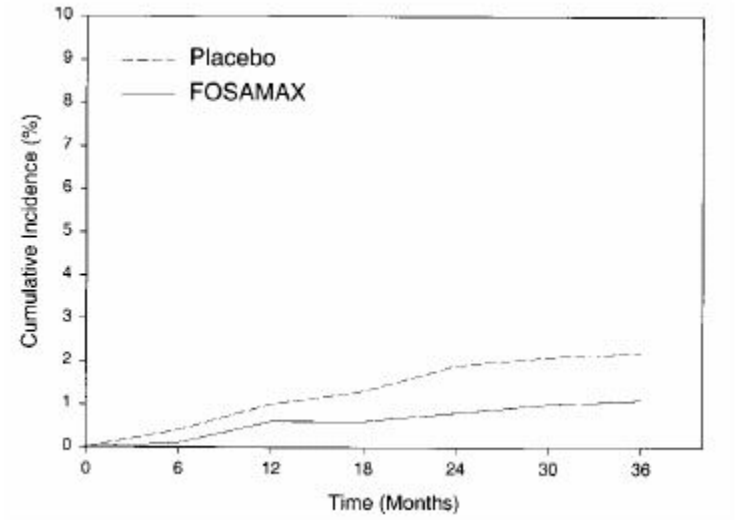


Figure 1: Cumulative Incidence of Hip Fractures in the Three-Year Study of FIT (patients with radiographic vertebral fracture at baseline)

Fracture Intervention Trial: Four-Year Study (patients with low bone mass but without a baseline radiographic vertebral fracture)
This randomized, double-blind, placebo-controlled, 4432-patient study (FOSAMAX, n=2214; placebo, n=2218) further investigated the reduction in fracture incidence due to FOSAMAX. The intent of the study was to recruit women with osteoporosis, defined as a baseline femoral neck BMD at least two standard deviations below the mean for young adult women. However, due to subsequent revisions to the normative values for femoral neck BMD, 31% of patients were found not to meet this entry criterion and thus this study included both osteoporotic and non-osteoporotic women. The results are shown in Table 7 below for the patients with osteoporosis.

Table 7: Effect of FOSAMAX on Fracture Incidence in Osteoporotic* Patients in the Four-Year Study of FIT (patients without vertebral fracture at baseline)

	Percent of Patients			
	FOSAMAX (n=1545)	Placebo (n=1521)	Absolute Reduction in Fracture Incidence	Relative Reduction in Fracture Risk (%)
Patients with:				
Vertebral fractures (diagnosed by X-ray)†				
≥1 new vertebral fracture	2.5	4.8	2.3	48‡
≥2 new vertebral fractures	0.1	0.6	0.5	78§
Clinical (symptomatic) fractures				
Any clinical (symptomatic) fracture	12.9	16.2	3.3	22¶
≥1 clinical (symptomatic) vertebral fracture	1.0	1.6	0.6	41 (NS)#
Hip fracture	1.0	1.4	0.4	29 (NS)#
Wrist (forearm) fracture	3.9	3.8	-0.1	NS#

*Baseline femoral neck BMD at least 2 SD below the mean for young adult women
†Number evaluable for vertebral fractures: FOSAMAX, n=1426; placebo, n=1428
‡p<0.001
§p=0.035
¶p=0.01
#Not significant. This study was not powered to detect differences at these sites.

Fracture Results Across Studies
In the Three-Year Study of FIT, FOSAMAX reduced the percentage of women experiencing at least one new radiographic vertebral fracture from 15.0% to 7.9% (47% relative risk reduction, p<0.001); in the Four-Year Study of FIT, the percentage was reduced from 3.8% to 2.1% (44% relative risk reduction, p=0.001); and in the combined U.S./Multinational studies, from 6.2% to 3.2% (48% relative risk reduction, p=0.034).
FOSAMAX reduced the percentage of women experiencing multiple (two or more) new vertebral fractures from 4.2% to 0.6% (87% relative risk reduction, p<0.001) in the combined U.S./Multinational studies and from 4.9% to 0.5% (90% relative risk reduction, p<0.001) in the Three-Year Study of FIT. In the Four-Year Study of FIT, FOSAMAX reduced the percentage of osteoporotic women experiencing multiple vertebral fractures from 0.6% to 0.1% (78% relative risk reduction, p=0.035).
Thus, FOSAMAX reduced the incidence of radiographic vertebral fractures in osteoporotic women whether or not they had a previous radiographic vertebral fracture.
FOSAMAX, over a three- or four-year period, was associated with statistically significant reductions in loss of height vs. placebo in patients with and without baseline radiographic vertebral fractures. At the end of the FIT studies the between-treatment group differences were 3.2 mm in the Three-Year Study and 1.3 mm in the Four-Year Study.
Effect on Bone Mineral Density
The efficacy of FOSAMAX 10 mg once daily in postmenopausal women with osteoporosis (lumbar spine bone mineral density [BMD] of at least 2 standard deviations below the premenopausal mean) was demonstrated in four double-blind, placebo-controlled clinical studies of two or three years' duration. These included two three-year, multicenter studies of virtually identical design, one performed in the United States (U.S.) and the other in 15 different countries (Multinational), which enrolled 478 and 516 patients, respectively. Figure 2 shows the mean increases in BMD of the lumbar spine, femoral neck, and trochanter in patients receiving FOSAMAX 10 mg/day relative to placebo-treated patients at three years for each of these studies.

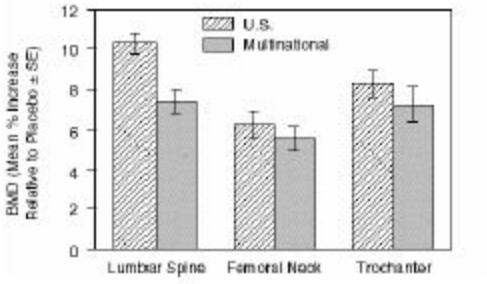


Figure 2: Osteoporosis Treatment Studies in Postmenopausal Women: Increase in BMD: FOSAMAX 10 mg/day at Three Years

At three years significant increases in BMD, relative both to baseline and placebo, were seen at each measurement site in each study in patients who received FOSAMAX 10 mg/day. Total body BMD also increased significantly in each study, suggesting that the increases in bone mass of the spine and hip did not occur at the expense of other skeletal sites. Increases in BMD were evident as early as three months and continued throughout the three years of treatment. (See figure 3 for lumbar spine results.) In the two-year extension of these studies, treatment of 147 patients with FOSAMAX 10 mg/day resulted in continued increases in BMD at the lumbar spine and trochanter (absolute additional increases between years 3 and 5: lumbar spine, 0.94%; trochanter, 0.88%). BMD at the femoral neck, forearm and total body were maintained. FOSAMAX was similarly effective regardless of age, race, baseline rate of bone turnover, and baseline BMD in the range studied (at least 2 standard deviations below the premenopausal mean).

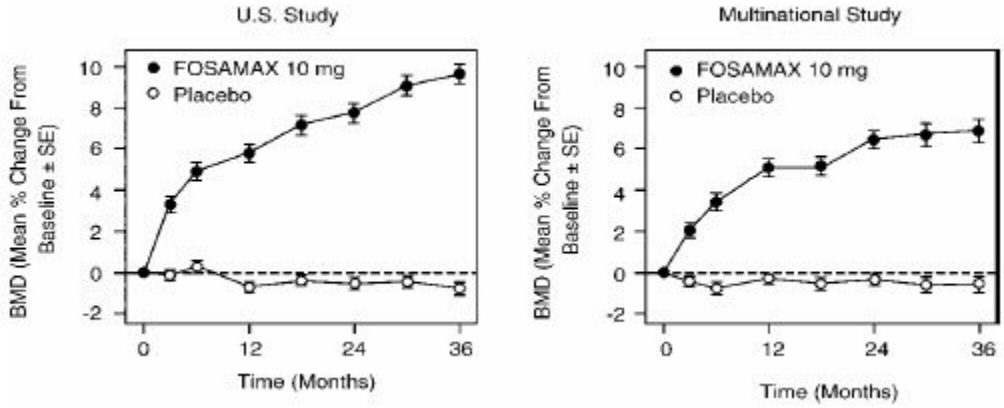


Figure 3: Osteoporosis Treatment Studies in Postmenopausal Women: Time Course of Effect of FOSAMAX 10 mg/day Versus Placebo: Lumbar Spine BMD Percent Change From Baseline

In patients with postmenopausal osteoporosis treated with FOSAMAX 10 mg/day for one or two years, the effects of treatment withdrawal were assessed. Following discontinuation, there were no further increases in bone mass and the rates of bone loss were similar to those of the placebo groups.

The therapeutic equivalence of once weekly FOSAMAX 70 mg (n=519) and FOSAMAX 10 mg daily (n=370) was demonstrated in a one-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary analysis of completers, the mean increases from baseline in lumbar spine BMD at one year were 5.1% (4.8, 5.4%; 95% CI) in the 70-mg once-weekly group (n=440) and 5.4% (5.0, 5.8%; 95% CI) in the 10-mg daily group (n=330). The two treatment groups were also similar with regard to BMD increases at other skeletal sites. The results of the intention-to-treat analysis were consistent with the primary analysis of completers.

Bone Histology

Bone histology in 270 postmenopausal patients with osteoporosis treated with FOSAMAX at doses ranging from 1 to 20 mg/day for one, two, or three years revealed normal mineralization and structure, as well as the expected decrease in bone turnover relative to placebo. These data, together with the normal bone histology and increased bone strength observed in rats and baboons exposed to long-term alendronate treatment, support the conclusion that bone formed during therapy with FOSAMAX is of normal quality.

Concomitant Use with Estrogen Hormone Replacement Therapy

The effects on BMD of treatment with FOSAMAX 10 mg once daily and conjugated estrogen (0.625 mg/day) either alone or in combination were assessed in a two-year, double-blind, placebo-controlled study of hysterectomized postmenopausal osteoporotic women (n=425). At two years, the increases in lumbar spine BMD from baseline were significantly greater with the combination (8.3%) than with either estrogen or FOSAMAX alone (both 6.0%).

The effects on BMD when FOSAMAX was added to stable doses (for at least one year) of HRT (estrogen ± progestin) were assessed in a one-year, double-blind, placebo-controlled study in postmenopausal osteoporotic women (n=428). The addition of FOSAMAX 10 mg once daily to HRT produced, at one year, significantly greater increases in lumbar spine BMD (3.7%) vs. HRT alone (1.1%).
In these studies, significant increases or favorable trends in BMD for combined therapy compared with HRT alone were seen at the total hip, femoral neck, and trochanter. No significant effect was seen for total body BMD.
Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied.

14.2 Treatment to Increase Bone Mass in Men with Osteoporosis
The efficacy of FOSAMAX in men with hypogonadal or idiopathic osteoporosis was demonstrated in two clinical studies.
A two-year, double-blind, placebo-controlled, multicenter study of FOSAMAX 10 mg once daily enrolled a total of 241 men between the ages of 31 and 87 (mean, 63). All patients in the trial had either: 1) a BMD T-score ≤–2 at the femoral neck and ≤–1 at the lumbar spine, or 2) a baseline osteoporotic fracture and a BMD T-score ≤–1 at the femoral neck. At two years, the mean increases relative to placebo in BMD in men receiving FOSAMAX 10 mg/day were significant at the following sites: lumbar spine, 5.3%; femoral neck, 2.6%; trochanter, 3.1%; and total body, 1.6%. Treatment with FOSAMAX also reduced height loss (FOSAMAX, –0.6 mm vs. placebo, –2.4 mm).
A one-year, double-blind, placebo-controlled, multicenter study of once weekly FOSAMAX 70 mg enrolled a total of 167 men between the ages of 38 and 91 (mean, 66). Patients in the study had either: 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, 2) a BMD T-score ≤-2 at the lumbar spine and ≤-1 at the femoral neck, or 3) a baseline osteoporotic fracture and a BMD T-score ≤-1 at the femoral neck. At one year, the mean increases relative to placebo in BMD in men receiving FOSAMAX 70 mg once weekly were significant at the following sites: lumbar spine, 2.8%; femoral neck, 1.9%; trochanter, 2.0%; and total body, 1.2%. These increases in BMD were similar to those seen at one year in the 10 mg once-daily study.
In both studies, BMD responses were similar regardless of age (≥65 years vs. <65 years), gonadal function (baseline testosterone <9 ng/dL vs. ≥9 ng/dL), or baseline BMD (femoral neck and lumbar spine T-score ≤-2.5 vs. >-2.5).

16 HOW SUPPLIED/STORAGE AND HANDLING
No. 3870 — Tablets FOSAMAX PLUS D 70 mg/2800 IU are white to off-white, modified capsule-shaped tablets with code 710 on one side and an outline of a bone image on the other. They are supplied as follows:
NDC 0006-0710-44 unit of use blister packages of 4.
No. 6746 — Tablets FOSAMAX PLUS D 70 mg/5600 IU are white to off-white, modified rectangle-shaped tablets with code 270 on one side and an outline of a bone image on the other. They are supplied as follows:
NDC 0006-0270-44 unit of use blister packages of 4
NDC 0006-0270-21 unit dose packages of 20.
Storage
Store at 20-25°C (68-77°F), excursions between 15-30°C (59-86°F) are allowed. [See USP Controlled Room Temperature.] Protect from moisture and light. Store tablets in the original blister package until use.
Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
By:
FROSST IBERICA, S.A.
28805 Alcalá de Henares
Madrid, Spain
Issued March 2011
6013311
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17 PATIENT COUNSELING INFORMATION
[See FDA-Approved Medication Guide.]
Physicians should instruct their patients to read the Medication Guide before starting therapy with FOSAMAX PLUS D and to reread it each time the prescription is renewed.

17.1 Osteoporosis Recommendations, Including Calcium and Vitamin D Supplementation
Patients should be instructed to take supplemental calcium if intake is inadequate. Patients at increased risk for vitamin D insufficiency (e.g., over the age of 70 years, nursing home bound, or chronically ill) should be instructed to take additional vitamin D if needed *[see Dosage and Administration (2.3)]*. Patients with gastrointestinal malabsorption syndromes should be informed that

they may require additional vitamin D supplementation. Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as cigarette smoking and/or excessive alcohol consumption, if these factors exist.

17.2 Dosing Instructions

Patients should be instructed that the expected benefits of FOSAMAX PLUS D may only be obtained when it is taken with plain water the first thing upon arising for the day at least 30 minutes before the first food, beverage, or medication of the day. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of alendronate *[see Clinical Pharmacology (12.3)]*.

To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, patients should be instructed to swallow each tablet of FOSAMAX PLUS D with a full glass of water (6–8 oz) and not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take FOSAMAX PLUS D at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of esophageal problems. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking FOSAMAX PLUS D and consult their physician.

Patients should be instructed that if they miss a dose of FOSAMAX PLUS D, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one tablet once a week, as originally scheduled on their chosen day.

MEDICATION GUIDE

FOSAMAX® PLUS D (FOSS-ah-max PLUS D)
(*alendronate sodium/cholecalciferol*)
Tablets

Read the Medication Guide that comes with FOSAMAX® PLUS D before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about FOSAMAX PLUS D.

What is the most important information I should know about FOSAMAX PLUS D?

FOSAMAX PLUS D can cause serious side effects including:

1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Bone, joint, or muscle pain
4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

1. **Esophagus problems.**
   Some people who take FOSAMAX PLUS D may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

- **It is important that you take FOSAMAX PLUS D exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take FOSAMAX PLUS D?")**
- **Stop taking FOSAMAX PLUS D and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.**

2. **Low calcium levels in your blood (hypocalcemia).**
   FOSAMAX PLUS D may lower the calcium levels in your blood. If you have low blood calcium before you start taking FOSAMAX PLUS D, it may get worse during treatment. Your low blood calcium must be treated before you take FOSAMAX PLUS D. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

3. **Bone, joint, or muscle pain.**
   Some people who take FOSAMAX PLUS D develop severe bone, joint, or muscle pain.

4. **Severe jaw bone problems (osteonecrosis).**
   Severe jaw bone problems may happen when you take FOSAMAX PLUS D. Your doctor should examine your mouth before you start FOSAMAX PLUS D. Your doctor may tell you to see your dentist before you start FOSAMAX PLUS D. It is important for you to practice good mouth care during treatment with FOSAMAX PLUS D.

5. **Unusual thigh bone fractures.**
   Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is FOSAMAX PLUS D?

FOSAMAX PLUS D is a prescription medicine used to:

- Treat osteoporosis in women after menopause. FOSAMAX PLUS D helps increase bone mass and reduces the chance of having a hip or spinal fracture (break).
- Increase bone mass in men with osteoporosis.

FOSAMAX PLUS D should not be used to treat vitamin D deficiency.

It is not known how long FOSAMAX PLUS D works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if FOSAMAX PLUS D is still right for you.

FOSAMAX PLUS D is not for use in children.

Who should not take FOSAMAX PLUS D?

Do not take FOSAMAX PLUS D if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 30 minutes
- Have low levels of calcium in your blood
- Are allergic to FOSAMAX PLUS D or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking FOSAMAX PLUS D?

Before you start FOSAMAX PLUS D, be sure to talk to your doctor if you:

- Have problems with swallowing
- Have stomach or digestive problems
- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have sarcoidosis, leukemia, lymphoma. These conditions may cause changes in vitamin D.
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant or plan to become pregnant. It is not known if FOSAMAX PLUS D can harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if FOSAMAX PLUS D passes into your milk and may harm your baby.

Especially tell your doctor if you take:

- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how FOSAMAX PLUS D works.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How should I take FOSAMAX PLUS D tablet?

- Take FOSAMAX PLUS D exactly as your doctor tells you.
- **FOSAMAX PLUS D works only if taken on an empty stomach.**
- Take 1 dose of FOSAMAX PLUS D 1 time a week, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take FOSAMAX PLUS D while you are sitting or standing.
- Take your FOSAMAX PLUS D tablet with a full glass (6-8 oz) of plain water.

- **Do not chew or suck on a tablet of FOSAMAX PLUS D.**

- **Do not** take FOSAMAX PLUS D with mineral water, coffee, tea, soda, or juice.

- Do not take FOSAMAX PLUS D at bedtime.

After swallowing FOSAMAX PLUS D, wait at least 30 minutes:
- Before you lie down. You may sit, stand or walk, and do normal activities like reading.

- Before you take your first food or drink except for plain water.

- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take FOSAMAX PLUS D and after you eat your first food of the day.
If you miss a dose of FOSAMAX PLUS D, do not take it later in the day. Take your missed dose on the next morning after you remember and then return to your normal schedule. Do not take 2 doses on the same day.
If you take too much FOSAMAX PLUS D, call your doctor. Do not try to vomit. Do not lie down.
What are the possible side effects of FOSAMAX PLUS D?
FOSAMAX PLUS D may cause serious side effects.
- See **"What is the most important information I should know about FOSAMAX PLUS D?"**

The most common side effects of FOSAMAX PLUS D are:
- Stomach area (abdominal) pain

- Heartburn

- Constipation

- Diarrhea

- Upset stomach

- Pain in your bones, joints, or muscles

- Nausea

You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of FOSAMAX PLUS D. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How do I store FOSAMAX PLUS D?
- Store FOSAMAX PLUS D at room temperature, 68°F to 77°F (20°C to 25°C).

- Keep FOSAMAX PLUS D away from light.

- Keep FOSAMAX PLUS D package and tablets dry.

- Store FOSAMAX PLUS D in the original package.

Keep FOSAMAX PLUS D and all medicines out of the reach of children.
General information about the safe and effective use of FOSAMAX PLUS D.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FOSAMAX PLUS D for a condition for which it was not prescribed. Do not give FOSAMAX PLUS D to other people, even if they have the same symptoms you have. It may harm them.
This Medication Guide summarizes the most important information about FOSAMAX PLUS D. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about FOSAMAX PLUS D that is written for health professionals.
For more information, go to: www.fosamaxplusd.com or call 1-877-408-4699.
What are the ingredients in FOSAMAX PLUS D?
Active ingredients: alendronate sodium and cholecalciferol (vitamin D_3).
Inactive ingredients: cellulose, lactose, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
By:
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Madrid, Spain
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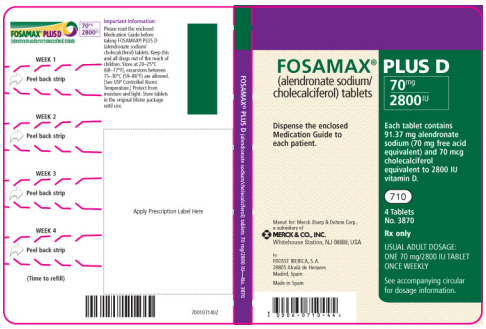
This Medication Guide has been approved by the U.S. Food and Drug Administration.

This is a representative sample of the packaging. Please see How Supplied section for a complete list of available packaging.

PRINCIPAL DISPLAY PANEL - BI FOLD CARD, OUTER 70 mg/2800 IU

FOSAMAX® PLUS D
(alendronate sodium/cholecalciferol) tablets
70 mg/2800 IU
Dispense the enclosed Medication Guide to each patient.
Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent) and 70 mcg cholecalciferol equivalent to 2800 IU vitamin D.
4 Tablets
No. 3870
Rx only
USUAL ADULT DOSAGE: ONE 70 mg/2800 IU TABLET ONCE WEEKLY
See accompanying circular for dosage information.
Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
By:
FROSST IBERICA, S. A.
28805 Alcalá de Henares
Madrid, Spain
Made in Spain



PRINCIPAL DISPLAY PANEL - BI FOLD CARD, OUTER 70 mg/5600 IU

FOSAMAX® PLUS D
(alendronate sodium/cholecalciferol) tablets
70 mg/5600 IU
Dispense the enclosed Medication Guide to each patient.
Each tablet contains 91.37 mg alendronate sodium (70 mg free acid equivalent) and 140 mcg cholecalciferol equivalent to 5600 IU vitamin D.
4 Tablets
No. 6746
Rx only
USUAL ADULT DOSAGE: ONE 70 mg/5600 IU TABLET ONCE WEEKLY
See accompanying circular for dosage information.
Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
By:
FROSST IBERICA, S. A.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Actonel safely and effectively. See full prescribing information for Actonel.

Actonel® (risedronate sodium) tablets
Initial U.S. Approval: 1998

RECENT MAJOR CHANGES

Indications and Usage [(1.5)	01/2011]
Warnings and Precautions [(5.5)	01/2011]

INDICATIONS AND USAGE

Actonel is a bisphosphonate indicated for:
- Treatment and prevention of postmenopausal osteoporosis (1.1)
- Treatment to increase bone mass in men with osteoporosis (1.2)
- Treatment and prevention of glucocorticoid-induced osteoporosis (1.3)
- Treatment of Paget's disease (1.4)

The optinal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis (1.5)

DOSAGE AND ADMINISTRATION

Must be taken with plain water (6 to 8 oz) at least 30 minutes before the first food or drink of the day; do not lie down for 30 minutes (2)
Treatment of Postmenopausal Osteoporosis: 5 mg daily, 35 mg once a week, 75 mg two consecutive days each month, 150 mg once a month (2.1)
Prevention of Postmenopausal Osteoporosis: 5 mg daily, 35 mg once a week (2.2)
Men with Osteoporosis: 35 mg once a week (2.3)
Glucocorticoid-Induced Osteoporosis: 5 mg daily (2.4)
Paget's Disease: 30 mg daily for 2 months (2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 5, 30, 35, 75, and 150 mg (3)

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia (4, 5.1)
- Inability to stand or sit upright for at least 30 minutes (4, 5.1)
- Hypocalcemia (4, 5.2)
- Known hypersensitivity to any component of this product (4, 6.2)

WARNINGS AND PRECAUTIONS

- Severe irritation of the upper gastrointestinal (GI) mucosa can occur. Dosing instructions should be followed and caution should be used in patients with active upper GI disease. Discontinue use if new or worsening symptoms occur (5.1)
- Hypocalcemia may worsen and must be corrected prior to use (5.2)
- Osteonecrosis of the jaw has been reported rarely (5.3)
- Severe bone, joint, or muscle pain may occur. Consider discontinuing use if severe symptoms develop (5.4, 6.2)
- Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture (5.5)

ADVERSE REACTIONS

Most common adverse reactions reported in >10% of patients treated with Actonel and with a higher frequency than placebo are: back pain, arthralgia, abdominal pain, and dyspepsia (6.1)
Hypersensitivity reactions (angioedema, generalized rash, bullous skin reactions), and eye inflammation (iritis, uveitis) have been reported rarely (6.2)
To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-521-8813 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Calcium, antacids, or oral medications containing divalent cations interfere with the absorption of Actonel (7.1)

USE IN SPECIFIC POPULATIONS

Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) (5.6, 8.6, 12.3)
Actonel is not indicated for use in pediatric patients (8.4)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 02/2011

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*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Postmenopausal Osteoporosis

Actonel is indicated for the treatment and prevention of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, Actonel reduces the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures [*see Clinical Studies (14.1, 14.2)*].

1.2 Osteoporosis in Men

Actonel is indicated for treatment to increase bone mass in men with osteoporosis.

1.3 Glucocorticoid-Induced Osteoporosis

Actonel is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoid treatment (daily dosage of ≥ 7.5 mg prednisone or equivalent) for chronic diseases. Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

1.4 Paget's Disease

Actonel is indicated for treatment of Paget's disease of bone in men and women.

1.5 Important Limitations of Use

The safety and effectiveness of Actonel for the treatment of osteoporosis are based on clinical data of three years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

2 DOSAGE AND ADMINISTRATION

Actonel should be taken at least 30 minutes before the first food or drink of the day other than water.
To facilitate delivery to the stomach, Actonel should be swallowed while the patient is in an upright position and with a full glass of plain water (6 to 8 oz). Patients should not lie down for 30 minutes after taking the medication [*see Warnings and Precautions (5.1)*].

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate [*see Warnings and Precautions (5.2)*]. Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of Actonel and should be taken at a different time of the day. Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min or in the elderly.

2.1 Treatment of Postmenopausal Osteoporosis
[*see Indications and Usage (1.1)*]
The recommended regimen is:
- one 5 mg tablet orally, taken daily

  or
- one 35 mg tablet orally, taken once a week

  or
- one 75 mg tablet orally, taken on two consecutive days for a total of two tablets each month

  or
- one 150 mg tablet orally, taken once a month

2.2 Prevention of Postmenopausal Osteoporosis
[*see Indications and Usage (1.1)*]
The recommended regimen is:
- one 5 mg tablet orally, taken daily

  or
- one 35 mg tablet orally, taken once a week

  or
- alternatively, one 75 mg tablet orally, taken on two consecutive days for a total of two tablets each month may be considered

  or
- alternatively, one 150 mg tablet orally, taken once a month may be considered

2.3 Treatment to Increase Bone Mass in Men with Osteoporosis
[*see Indications and Usage (1.2)*]
The recommended regimen is:
- one 35 mg tablet orally, taken once a week

2.4 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis
[*see Indications and Usage (1.3)*]
The recommended regimen is:
- one 5 mg tablet orally, taken daily

2.5 Treatment of Paget's Disease
[*see Indications and Usage (1.4)*]
The recommended treatment regimen is 30 mg orally once daily for 2 months. Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs, or if treatment fails to normalize serum alkaline phosphatase. For retreatment, the dose and duration of therapy are the same as for initial treatment. No data are available on more than 1 course of retreatment.

3 DOSAGE FORMS AND STRENGTHS
- 5 mg film-coated, oval, yellow tablet with RSN on 1 face and 5 mg on the other.
- 30 mg film-coated, oval, white tablet with RSN on 1 face and 30 mg on the other.
- 35 mg film-coated, oval, orange tablet with RSN on 1 face and 35 mg on the other.
- 75 mg film-coated, oval, pink tablet with RSN on 1 face and 75 mg on the other.
- 150 mg film-coated, oval, blue tablet with RSN on 1 face and 150 mg on the other.

4 CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia [*see Warnings and Precautions (5.1)*]
- Inability to stand or sit upright for at least 30 minutes [*see Dosage and Administration (2), Warnings and Precautions (5.1)*]
- Hypocalcemia [*see Warnings and Precautions (5.2)*]
- Known hypersensitivity to any component of this product [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Upper Gastrointestinal Adverse Reactions

Actonel, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Actonel is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers) [*see Contraindications (4), Adverse Reactions (6.1), Information for Patients (17.1)*].

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. In some cases, these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue Actonel and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates and/or who fail to swallow it with the recommended full glass (6 to 8 oz) of water, and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient [*see Dosage and Administration (2)*]. In patients who cannot comply with dosing instructions due to mental disability, therapy with Actonel should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

5.2 Mineral Metabolism

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Actonel therapy. Adequate intake of calcium and vitamin D is important in all patients, especially in patients with Paget's disease in whom bone turnover is significantly elevated [*see Contraindications (4), Adverse Reactions (6.1), Information for Patients (17.1)*].

5.3 Jaw Osteonecrosis

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including Actonel. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment [*see Adverse Reactions (6.2)*].

5.4 Musculoskeletal Pain

In postmarketing experience, there have been reports of severe and occasionally incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates [*see Adverse Reactions (6.2)*]. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are traverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete

fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

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

5.7 Glucocorticoid-Induced Osteoporosis
Before initiating Actonel treatment for the treatment and prevention of glucocorticoid-induced osteoporosis, the sex steroid hormonal status of both men and women should be ascertained and appropriate replacement considered.

5.8 Laboratory Test Interactions
Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with Actonel have not been performed.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of Postmenopausal Osteoporosis
Daily Dosing

The safety of Actonel 5 mg once daily in the treatment of postmenopausal osteoporosis was assessed in four randomized, double-blind, placebo-controlled multinational trials of 3232 women aged 38 to 85 years with postmenopausal osteoporosis. The duration of the trials was up to three years, with 1619 patients exposed to placebo and 1613 patients exposed to Actonel 5 mg. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H_2 antagonists were included in these clinical trials. All women received 1000 mg of elemental calcium plus vitamin D supplementation up to 500 IU per day if their 25-hydroxyvitamin D_3 level was below normal at baseline.

The incidence of all-cause mortality was 2.0% in the placebo group and 1.7% in the Actonel 5 mg daily group. The incidence of serious adverse events was 24.6% in the placebo group and 27.2% in the Actonel 5 mg group. The percentage of patients who withdrew from the study due to adverse events was 15.6% in the placebo group and 14.8% in the Actonel 5 mg group. Table 1 lists adverse events from the Phase 3 postmenopausal osteoporosis trials reported in ≥5% of patients. Adverse events are shown without attribution of causality.

Table 1 Adverse Events Occurring at a Frequency ≥5% in Either Treatment Group Combined Phase 3 Postmenopausal Osteoporosis Treatment Trials

Body System	**Placebo N = 1619 %**	**5 mg Actonel N = 1613 %**
Body as a Whole		
Infection	29.9	31.1
Back Pain	26.1	28.0
Accidental Injury	16.8	16.9
Pain	14.0	14.1
Abdominal Pain	9.9	12.2
Flu Syndrome	11.6	10.5
Headache	10.8	9.9
Asthenia	4.5	5.4
Neck Pain	4.7	5.4
Chest Pain	5.1	5.0
Allergic Reaction	5.9	3.8
Cardiovascular System		
Hypertension	9.8	10.5

Digestive System		
Constipation	12.6	12.9
Diarrhea	10.0	10.8
Dyspepsia	10.6	10.8
Nausea	11.2	10.5
Metabolic & Nutritional Disorders		
Peripheral Edema	8.8	7.7
Musculoskeletal System		
Arthralgia	22.1	23.7
Arthritis	10.1	9.6
Traumatic Bone Fracture	12.3	9.3
Joint Disorder	5.3	7.0
Myalgia	6.2	6.7
Bone Pain	4.8	5.3
Nervous System		
Dizziness	5.7	7.1
Depression	6.1	6.8
Insomnia	4.6	5.0
Respiratory System		
Bronchitis	10.4	10.0
Sinusitis	9.1	8.7
Rhinitis	5.1	6.2
Pharyngitis	5.0	6.0
Increased Cough	6.3	5.9
Skin and Appendages		
Rash	7.1	7.9
Special Senses		
Cataract	5.7	6.5
Urogenital System		
Urinary Tract Infection	10.4	11.1

Gastrointestinal Adverse Events: The incidence of adverse events in the placebo and Actonel 5 mg daily groups were: abdominal pain (9.9% versus 12.2%), diarrhea (10.0% versus 10.8%), dyspepsia (10.6% versus 10.8%), and gastritis (2.3% versus 2.7%). Duodenitis and glossitis have been reported uncommonly in the Actonel 5 mg daily group (0.1% to 1%). In patients with active upper gastrointestinal disease at baseline, the incidence of upper gastrointestinal adverse events was similar between the placebo and Actonel 5 mg daily groups.

Musculoskeletal Adverse Events: The incidence of adverse events in the placebo and Actonel 5 mg daily groups were: back pain (26.1% versus 28.0%), arthralgia (22.1% versus 23.7%), myalgia (6.2% versus 6.7%), and bone pain (4.8% versus 5.3%).

Laboratory Test Findings: Throughout the Phase 3 studies, transient decreases from baseline in serum calcium (<1%) and serum phosphate (<3%) and compensatory increases in serum PTH levels (<30%) were observed within 6 months in patients in osteoporosis clinical trials treated with Actonel 5 mg once daily. There were no significant differences in serum calcium, phosphate, or PTH levels between placebo and Actonel 5 mg once daily at 3 years. Serum calcium levels below 8 mg/dL were observed in 18 patients, 9 (0.5%) in each treatment arm (placebo and Actonel 5 mg once daily). Serum phosphorus levels below 2 mg/dL were observed in 14 patients, 3 (0.2%) treated with placebo and 11 (0.6%) treated with Actonel 5 mg once daily. There have been rare reports (<0.1%) of abnormal liver function tests.

Endoscopic Findings: In the Actonel clinical trials, endoscopic evaluation was encouraged in any patient with moderate-to-severe gastrointestinal complaints, while maintaining the blind. Endoscopies were performed on equal numbers of patients between the placebo and treated groups [75 (14.5%) placebo; 75 (11.9%) Actonel]. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (51% placebo; 39% Actonel).

Once-a-Week Dosing

The safety of Actonel 35 mg once-a-week in the treatment of postmenopausal osteoporosis was assessed in a 1-year, double-blind, multicenter study comparing Actonel 5 mg daily and Actonel 35 mg once-a-week in postmenopausal women aged 50 to 95 years. The duration of the trials was one year, with 480 patients exposed to ACTONEL 5 mg daily and 485 exposed to Actonel 35 mg once-a-week. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H_2 antagonists were included in these clinical trials. All women received 1000 mg of elemental calcium plus vitamin D supplementation up to 500 IU per day if their 25-hydroxyvitamin D_3 level was below normal at baseline.

The incidence of all-cause mortality was 0.4% in the Actonel 5 mg daily group and 1.0% in the Actonel 35 mg once-a-week group. The incidence of serious adverse events was 7.1% in the Actonel 5 mg daily group and 8.2% in the Actonel 35 mg once-a-week group. The percentage of patients who withdrew from the study due to adverse events was 11.9% in the Actonel 5 mg daily group and 11.5% in the Actonel 35 mg once-a-week group. The overall safety and tolerability profiles of the two dosing regimens were similar.

Gastrointestinal Adverse Events: The incidence of gastrointestinal adverse events was similar between the Actonel 5 mg daily group and the Actonel 35 mg once-a-week group: dyspepsia (6.9% versus 7.6%), diarrhea (6.3% versus 4.9%), and abdominal pain (7.3% versus 7.6%).

Musculoskeletal Adverse Events: Arthralgia was reported in 11.5% of patients in the Actonel 5 mg daily group and 14.2% of patients in the Actonel 35 mg once-a-week group. Myalgia was reported by 4.6% of patients in the Actonel 5 mg daily group and 6.2% of patients in the Actonel 35 mg once-a-week group.

Laboratory Test Findings: The mean percent changes from baseline at 12 months were similar between the Actonel 5 mg daily and Actonel 35 mg once-a-week groups, respectively, for serum calcium (0.4% versus 0.7%), phosphate (-3.8% versus -2.6%) and PTH (6.4% versus 4.2%).

Monthly Dosing

Two Consecutive Days per Month

The safety of Actonel 75 mg administered on two consecutive days per month for the treatment of postmenopausal osteoporosis was assessed in a double-blind, multicenter study in postmenopausal women aged 50 to 86 years. The duration of the trial was two years; 613 patients were exposed to Actonel 5 mg daily and 616 were exposed to Actonel 75 mg two consecutive days per month. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H_2 antagonists were included in this clinical trial. All women received 1000 mg of elemental calcium plus 400 to 800 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 1.0% for the Actonel 5 mg daily group and 0.5% for the Actonel 75 mg two consecutive days per month group. The incidence of serious adverse events was 10.8% in the Actonel 5 mg daily group and 14.4% in the Actonel 75 mg two consecutive days per month group. The percentage of patients who withdrew from treatment due to adverse events was 14.2% in the Actonel 5 mg daily group and 13.0% in the Actonel 75 mg two consecutive days per month group. The overall safety and tolerability profiles of the two dosing regimens were similar.

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of acute phase reaction was 3.6% of patients on Actonel 5 mg daily and 7.6% of patients on Actonel 75 mg two consecutive days per month. These incidence rates are based on reporting of any of 33 acute phase reaction-like symptoms within 5 days of the first dose. Fever or influenza-like illness with onset within the same period were reported by 0.0% of patients on Actonel 5 mg daily and 0.6% of patients on Actonel 75 mg two consecutive days per month.

Gastrointestinal Adverse Events: The Actonel 75 mg two consecutive days per month group resulted in a higher incidence of discontinuation due to vomiting (1.0% versus 0.2%) and diarrhea (1.0% versus 0.3%) compared to the Actonel 5 mg daily group. Most of these events occurred within a few days of dosing.

Ocular Adverse Events: None of the patients treated with Actonel 75 mg two consecutive days per month reported ocular inflammation such as uveitis, scleritis, or iritis; 1 patient treated with Actonel 5 mg daily reported uveitis.

Laboratory Test Findings: When Actonel 5 mg daily and Actonel 75 mg two consecutive days per month were compared in postmenopausal women with osteoporosis, the mean percent changes from baseline at 24 months were 0.2% and 0.8% for serum calcium, -1.9% and -1.3% for phosphate, and -10.4% and -17.2% for PTH, respectively. Compared to the Actonel 5 mg daily group, Actonel 75 mg two consecutive days per month resulted in a slightly higher incidence of hypocalcemia at the end of the first month of treatment (4.5% versus 3.0%). Thereafter, the incidence of hypocalcemia with these regimens was similar at approximately 2%.

Once-a-Month

The safety of Actonel 150 mg administered once a month for the treatment of postmenopausal osteoporosis was assessed in a double-blind, multicenter study in postmenopausal women aged 50 to 88 years. The duration of the trial was one year, with 642 patients exposed to Actonel 5 mg daily and 650 exposed to Actonel 150 mg once-a-month. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H_2 antagonists were included in this clinical trial. All women received 1000 mg of elemental calcium plus up to 1000 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 0.5% for the Actonel 5 mg daily group and 0.0% for the Actonel 150 mg once-a-month group. The incidence of serious adverse events was 4.2% in the Actonel 5 mg daily group and 6.2% in the Actonel 150 mg once-a-month group. The percentage of patients who withdrew from treatment due to adverse events was 9.5% in the Actonel 5 mg daily group and 8.6% in the Actonel 150 mg once-a-month group. The overall safety and tolerability profiles of the two dosing regimens were similar.

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of acute phase reaction was 1.1% in the Actonel 5 mg daily group and 5.2% in the Actonel 150 mg once-a-month group. These incidence rates are based on reporting of any of 33 acute phase reaction-like symptoms within 3 days of the first dose and for a duration of 7 days or less. Fever or influenza-like illness with onset within the same period were reported by 0.2% of patients on Actonel 5 mg daily and 1.4% of patients on Actonel 150 mg once-a-month.

Gastrointestinal Adverse Events: A greater percentage of patients experienced diarrhea with Actonel 150 mg once-a-month compared to 5 mg daily (8.2% versus 4.7%, respectively). The Actonel 150 mg once-a-month group resulted in a higher incidence of discontinuation due to abdominal pain upper (2.5% versus 1.4%) and diarrhea (0.8% versus 0.0%) compared to the Actonel 5 mg daily regimen. All of these events occurred within a few days of the first dose. The incidence of vomiting that led to discontinuation was the same in both groups (0.3% versus 0.3%).

Ocular Adverse Events: None of the patients treated with Actonel 150 mg once-a-month reported ocular inflammation such as uveitis, scleritis, or iritis; 2 patients treated with Actonel 5 mg daily reported iritis.

Laboratory Test Findings: When Actonel 5 mg daily and Actonel 150 mg once-a-month were compared in postmenopausal women with osteoporosis, the mean percent changes from baseline at 12 months were 0.1% and 0.3% for serum calcium, -2.3% and -2.3% for phosphate, and 8.3% and 4.8% for PTH, respectively. Compared to the Actonel 5 mg daily regimen, Actonel 150 mg once-a-month resulted in a slightly higher incidence of hypocalcemia at the end of the first month of treatment (0.2% versus 2.2%). Thereafter, the incidence of hypocalcemia with these regimens was similar at approximately 2%.

Prevention of Postmenopausal Osteoporosis

Daily Dosing

The safety of Actonel 5 mg daily in the prevention of postmenopausal osteoporosis was assessed in two randomized, double-blind, placebo-controlled trials. In one study of postmenopausal women aged 37 to 82 years without osteoporosis, the use of estrogen replacement therapy in both placebo- and Actonel-treated patients was included. The duration of the trial was one year, with 259 exposed to placebo and 261 patients exposed to Actonel 5 mg. The second study included postmenopausal women aged 44 to 63 years without osteoporosis. The duration of the trial was one year, with 125 exposed to placebo and 129 patients exposed to Actonel 5 mg. All women received 1000 mg of elemental calcium per day.

In the trial with estrogen replacement therapy, the incidence of all-cause mortality was 1.5% for the placebo group and 0.4% for the Actonel 5 mg group. The incidence of serious adverse events was 8.9% in the placebo group and 5.4% in the Actonel 5 mg group. The percentage of patients who withdrew from treatment due to adverse events was 18.9% in the placebo group and 10.3% in the Actonel 5 mg group. Constipation was reported by 1.9% of the placebo group and 6.5% of Actonel 5 mg group.

In the second trial, the incidence of all-cause mortality was 0.0% for both groups. The incidence of serious adverse events was 17.6% in the placebo group and 9.3% in the Actonel 5 mg group. The percentage of patients who withdrew from treatment due to adverse events was 6.4% in the placebo group and 5.4% in the Actonel 5 mg group. Nausea was reported by 6.4% of patients in the placebo group and 13.2% of patients in the Actonel 5 mg group.

Once-a-Week Dosing

There were no deaths in a 1-year, double-blind, placebo-controlled study of Actonel 35 mg once a week for prevention of bone loss in 278 postmenopausal women without osteoporosis. More treated subjects on Actonel reported arthralgia (placebo 7.8%; Actonel 13.9%), myalgia (placebo 2.1%; Actonel 5.1%), and nausea (placebo 4.3%; Actonel 7.3%) than subjects on placebo.

Treatment to Increase Bone Mass in Men with Osteoporosis
In a 2-year, double-blind, multicenter study, 284 men with osteoporosis were treated with placebo (N = 93) or Actonel 35 mg once-a-week (N = 191). The overall safety and tolerability profile of Actonel in men with osteoporosis was similar to the adverse events reported in the Actonel postmenopausal osteoporosis clinical trials, with the addition of benign prostatic hyperplasia (placebo 3%; Actonel 35 mg 5%), nephrolithiasis (placebo 0%; Actonel 35 mg 3%), and arrhythmia (placebo 0%; Actonel 35 mg 2%).

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis
The safety of Actonel 5 mg daily in the treatment and prevention of glucocorticoid-induced osteoporosis was assessed in two randomized, double-blind, placebo-controlled multinational trials of 344 patients [male (123) and female (221)] aged 18 to 85 years who had recently initiated oral glucocorticoid therapy (≤ 3 months, prevention study) or were on long-term oral glucocorticoid therapy (≥ 6 months, treatment study). The duration of the trials was one year, with 170 patients exposed to placebo and 174 patients exposed to Actonel 5 mg daily. Patients in one study received 1000 mg elemental calcium plus 400 IU of vitamin D supplementation per day; patients in the other study received 500 mg calcium supplementation per day.

The incidence of all-cause mortality was 2.9% in the placebo group and 1.1% in the Actonel 5 mg daily group. The incidence of serious adverse events was 33.5% in the placebo group and 30.5% in the Actonel 5 mg daily group. The percentage of patients who withdrew from the study due to adverse events was 8.8% in the placebo group and 7.5% in the Actonel 5 mg daily group. Back pain was reported in 8.8% of patients in the placebo group and 17.8% of patients in the Actonel 5 mg daily group. Arthralgia was reported in 14.7% of patients in the placebo group and 24.7% of patients in the Actonel 5 mg daily group.

Treatment of Paget's Disease
Actonel has been studied in 392 patients with Paget's disease of bone. As in trials of Actonel for other indications, the adverse experiences reported in the Paget's disease trials have generally been mild or moderate, have not required discontinuation of treatment, and have not appeared to be related to patient age, gender, or race.

The safety of Actonel was assessed in a randomized, double-blind, active-controlled study of 122 patients aged 34 to 85 years. The duration of the trial was 540 days, with 61 patients exposed to Actonel and 61 patients exposed to Didronel®. The adverse event profile was similar for Actonel and Didronel: 6.6% (4/61) of patients treated with Actonel 30 mg daily for 2 months discontinued treatment due to adverse events, compared to 8.2% (5/61) of patients treated with Didronel 400 mg daily for 6 months. Table 2 lists adverse events reported in ≥5% of Actonel-treated patients in Phase 3 Paget's disease trials. Adverse events shown are considered to be possibly or probably causally related in at least one patient.

Table 2 Adverse Events Reported in ≥5% of Actonel-Treated Patients* in Phase 3 Paget's Disease Trials

Body System	30 mg/day x 2 months Actonel % (N = 61)	400 mg/day x 6 months Didronel % (N = 61)
Body as a Whole		
Flu Syndrome	9.8	1.6
Chest Pain	6.6	3.3
Gastrointestinal		
Diarrhea	19.7	14.8
Abdominal Pain	11.5	8.2
Nausea	9.8	9.8
Constipation	6.6	8.2
Metabolic and Nutritional Disorders		
Peripheral Edema	8.2	6.6
Musculoskeletal		
Arthralgia	32.8	29.5
Nervous		
Headache	18.0	16.4
Dizziness	6.6	4.9
Skin and Appendages		
Rash	11.5	8.2

*Considered to be possibly or probably causally related in at least one patient.

Gastrointestinal Adverse Events: During the first year of the study (treatment and nontreatment follow-up), the proportion of patients who reported upper gastrointestinal adverse events was similar between the treatment groups; no patients reported severe upper gastrointestinal adverse events. The incidence of diarrhea was 19.7% in the Actonel group and 14.8% in the Didronel group; none were serious or resulted in withdrawal.

Ocular Adverse Events: Three patients who received Actonel 30 mg daily experienced acute iritis in 1 supportive study. All 3 patients recovered from their events; however, in 1 of these patients, the event recurred during Actonel treatment and again during treatment with pamidronate. All patients were effectively treated with topical steroids.

6.2 Postmarketing Experience

Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity Reactions

Hypersensitivity and skin reactions have been reported rarely, including angioedema, generalized rash and bullous skin reactions, some severe.

Gastrointestinal Adverse Events

Events involving upper gastrointestinal irritation, such as esophagitis and esophageal or gastric ulcers, have been reported [*see Warnings and Precautions (5.1)*].

Musculoskeletal Pain

Bone, joint, or muscle pain, described as severe or incapacitating, have been reported rarely [*see Warnings and Precautions (5.4)*].

Eye Inflammation

Reactions of eye inflammation including iritis and uveitis have been reported rarely.

Jaw Osteonecrosis

Osteonecrosis of the jaw has been reported rarely [*see Warnings and Precautions (5.3)*].

7 DRUG INTERACTIONS

No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (e.g., Cytochrome P450).

7.1 Calcium Supplements/Antacids

Co-administration of Actonel and calcium, antacids, or oral medications containing divalent cations will interfere with the absorption of Actonel.

7.2 Hormone Replacement Therapy

One study of about 500 early postmenopausal women has been conducted to date in which treatment with Actonel 5 mg daily plus estrogen replacement therapy was compared to estrogen replacement therapy alone. Exposure to study drugs was approximately 12 to 18 months and the primary endpoint was change in BMD. If considered appropriate, Actonel may be used concomitantly with hormone replacement therapy.

7.3 Aspirin/Nonsteroidal Anti-Inflammatory Drugs

Of over 5700 patients enrolled in the Actonel Phase 3 osteoporosis studies, aspirin use was reported by 31% of patients, 24% of whom were regular users (3 or more days per week). Forty-eight percent of patients reported NSAID use, 21% of whom were regular users. Among regular aspirin or NSAID users, the incidence of upper gastrointestinal adverse experiences in placebo-treated patients (24.8%) was similar to that in Actonel-treated patients (24.5%).

7.4 H_2 Blockers and Proton Pump Inhibitors (PPIs)

Of over 5700 patients enrolled in the Actonel Phase 3 osteoporosis studies, 21% used H_2 blockers and/or PPIs. Among these patients, the incidence of upper gastrointestinal adverse experiences in the placebo-treated patients was similar to that in Actonel-treated patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over periods of weeks to years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been studied.

In animal studies, pregnant rats received risedronate sodium during organogenesis at doses 1 to 26 times the human dose of 30 mg/day. Survival of neonates was decreased in rats treated during gestation with oral doses approximately 5 times the human dose and body weight was decreased in neonates from dams treated with approximately 26 times the human dose. The number of fetuses exhibiting incomplete ossification of sternebrae or skull from dams treated with approximately 2.5 times the human dose was significantly increased compared to controls. Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses approximately 5 times the human dose. A low incidence of cleft palate was observed in fetuses from female rats treated with oral doses approximately equal to the human dose. The relevance of this finding to human use of Actonel is unclear.
No significant fetal ossification effects were seen in rabbits treated with oral doses approximately 7 times the human dose (the highest dose tested). However, 1 of 14 litters were aborted and 1 of 14 litters were delivered prematurely.
Similar to other bisphosphonates, treatment during mating and gestation with doses of risedronate sodium approximately the same as the 30 mg/day human dose resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.
Dosing multiples provided above are based on the recommended human dose of 30 mg/day and normalized using body surface area (mg/m^2). Actual animal doses were 3.2, 7.1 and 16 mg/kg/day in the rat and 10 mg/kg/day in the rabbit.

8.3 Nursing Mothers
Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period post-dosing, indicating a small degree of lacteal transfer. It is not known whether Actonel is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Actonel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Actonel is not indicated for use in pediatric patients.
The safety and effectiveness of risedronate was assessed in a one-year, randomized, double-blind, placebo controlled study of 143 pediatric patients (94 received risedronate) with osteogenesis imperfecta (OI). The enrolled population was predominantly patients with mild osteogenesis imperfecta (85% Type-I), aged 4 to <16 years, 50% male and 82% Caucasian, with a mean lumbar spine BMD Z-score of -2.08 (2.08 standard deviations below the mean for age-matched controls). Patients received either a 2.5 mg (≤30 kg body weight) or 5 mg (>30 kg body weight) daily oral dose. After one year, an increase in lumbar spine BMD in the risedronate group compared to the placebo group was observed. However, treatment with risedronate did not result in a reduction in the risk of fracture in pediatric patients with osteogenesis imperfecta. In Actonel-treated subjects, no mineralization defects were noted in paired bone biopsy specimens obtained at baseline and month 12.
The overall safety profile of risedronate in OI patients treated for up to 12 months was generally similar to that of adults with osteoporosis. However, there was an increased incidence of vomiting compared to placebo. In this study, vomiting was observed in 15% of children treated with risedronate and 6% of patients treated with placebo. Other adverse events reported in ≥10% of patients treated with risedronate and with a higher frequency than placebo were: pain in the extremity (21% with risedronate versus 16% with placebo), headache (20% versus 8%), back pain (17% versus 10%), pain (15% versus 10%), upper abdominal pain (11% versus 8%), and bone pain (10% versus 4%).

8.5 Geriatric Use
Of the patients receiving Actonel in postmenopausal osteoporosis studies [*see Clinical Studies (14)*], 47% were between 65 and 75 years of age, and 17% were over 75. The corresponding proportions were 26% and 11% in glucocorticoid-induced osteoporosis trials, and 40% and 26% in Paget's disease trials. No overall differences in efficacy between geriatric and younger patients were observed in these studies. In the male osteoporosis trial, 28% of patients receiving Actonel were between 65 and 75 years of age and 9% were over 75. The lumbar spine BMD response for Actonel compared to placebo was 5.6% for subjects <65 years and 2.9% for subjects ≥65 years. No overall differences in safety between geriatric and younger patients were observed in the Actonel trials, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min.

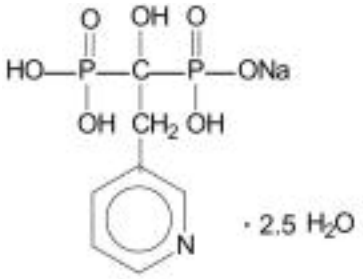
8.7 Hepatic Impairment
No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in human liver preparations. Dosage adjustment is unlikely to be needed in patients with hepatic impairment.

10 OVERDOSAGE
Decreases in serum calcium and phosphorus following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients. Milk or antacids containing calcium should be given to bind Actonel and reduce absorption of the drug.

In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug. Standard procedures that are effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.
Lethality after single oral doses was seen in female rats at 903 mg/kg and male rats at 1703 mg/kg. The minimum lethal dose in mice and rabbits was 4000 mg/kg and 1000 mg/kg, respectively. These values represent 320 to 620 times the 30 mg human dose based on surface area (mg/m^2).

11 DESCRIPTION

Actonel (risedronate sodium) tablets is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each Actonel tablet for oral administration contains the equivalent of 5, 30, 35, 75, or 150 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. The empirical formula for risedronate sodium hemi-pentahydrate is $C_7H_{10}NO_7P_2Na \cdot 2.5\ H_2O$. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt. The chemical structure of risedronate sodium hemi-pentahydrate is the following:



Molecular Weight:	
Anhydrous:	305.10
Hemi-pentahydrate:	350.13

Risedronate sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions, and essentially insoluble in common organic solvents.
Inactive Ingredients
All dose strengths contain: crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.
Dose strength-specific ingredients include: 5 mg—ferric oxide yellow, lactose monohydrate; 30 mg—lactose monohydrate; 35 mg—ferric oxide red, ferric oxide yellow, lactose monohydrate; 75 mg—ferric oxide red; 150 mg—FD&C blue #2 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Actonel has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, Actonel inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (e.g., lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that Actonel treatment reduces bone turnover (activation frequency, i.e., the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

12.2 Pharmacodynamics

Actonel treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of Actonel to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone-specific alkaline phosphatase (a marker of bone formation). At the 5 mg dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone-specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years. Bone turnover is decreased as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1-year study comparing daily versus weekly oral dosing regimens of Actonel for the treatment of osteoporosis in postmenopausal women, Actonel 5 mg daily and Actonel 35 mg once-a-week decreased urinary collagen cross-linked N-telopeptide by 60% and 61%, respectively. In addition, serum bone-specific alkaline phosphatase was also reduced by 42% and 41% in the Actonel 5 mg daily and Actonel 35 mg once-a-week groups, respectively. When postmenopausal women with osteoporosis were treated for 1 year with Actonel 5 mg daily or Actonel 75 mg two consecutive days per month, urinary collagen cross-linked N-telopeptide was decreased by 54% and 52%, respectively, and serum bone-specific alkaline phosphatase was reduced

by 36% and 35%, respectively. In a 1–year study comparing Actonel 5 mg daily versus Actonel 150 mg once-a-month in women with postmenopausal osteoporosis, urinary collagen cross-linked N-telopeptide was decreased by 52% and 49%, respectively, and serum bone-specific alkaline phosphatase was reduced by 31% and 32%, respectively.

Osteoporosis in Men

In a 2-year study of men with osteoporosis, treatment with Actonel 35 mg once-a-week resulted in a mean decrease from baseline compared to placebo of 16% (placebo 20%; Actonel 35 mg 37%) for the bone resorption marker urinary collagen cross-linked N-telopeptide, 45% (placebo -6%; Actonel 35 mg 39%) for the bone resorption marker serum C-telopeptide, and 27% (placebo -2%; Actonel 35 mg 25%) for the bone formation marker serum bone-specific alkaline phosphatase.

Glucocorticoid-Induced Osteoporosis

Osteoporosis with glucocorticoid use occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. Actonel decreases bone resorption without directly inhibiting bone formation.

In two 1-year clinical trials in the treatment and prevention of glucocorticoid-induced osteoporosis, Actonel 5 mg decreased urinary collagen cross-linked N-telopeptide (a marker of bone resorption), and serum bone-specific alkaline phosphatase (a marker of bone formation) by 50% to 55% and 25% to 30%, respectively, within 3 to 6 months after initiation of therapy.

Paget's Disease

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disordered bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

In pagetic patients treated with Actonel 30 mg daily for 2 months, bone turnover returned to normal in a majority of patients as evidenced by significant reductions in serum alkaline phosphatase (a marker of bone formation), and in urinary hydroxyproline/ creatinine and deoxypyridinoline/creatinine (markers of bone resorption).

12.3 Pharmacokinetics

Absorption

Based on simultaneous modeling of serum and urine data, peak absorption after an oral dose is achieved at ~ 1 hour (T_{max}) and occurs throughout the upper gastrointestinal tract. The fraction of the dose absorbed is independent of dose over the range studied (single dose, from 2.5 mg to 30 mg; multiple dose, from 2.5 mg to 5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30 mg tablet is 0.63% (90% CI: 0.54% to 0.75%) and is comparable to a solution.

Food Effect

The extent of absorption of a 30 mg dose (three 10 mg tablets) when administered 0.5 hours before breakfast is reduced by 55% compared to dosing in the fasting state (no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces the extent of absorption by 30% compared to dosing in the fasting state. Dosing either 0.5 hours prior to breakfast or 2 hours after dinner (evening meal) results in a similar extent of absorption. Actonel is effective when administered at least 30 minutes before breakfast.

Distribution

The mean steady-state volume of distribution for risedronate is 13.8 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was in the range of 0.001% to 0.01%.

Metabolism

There is no evidence of systemic metabolism of risedronate.

Excretion

In young healthy subjects, approximately half of the absorbed dose of risedronate was excreted in urine within 24 hours, and 85% of an intravenous dose was recovered in the urine over 28 days. Based on simultaneous modeling of serum and urine data, mean renal clearance was 105 mL/min (CV = 34%) and mean total clearance was 122 mL/min (CV = 19%), with the difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. In osteopenic postmenopausal women, the terminal exponential half-life was 561 hours, mean renal clearance was 52 mL/min (CV = 25%), and mean total clearance was 73 mL/min (CV = 15%).

Specific Populations

Pediatric: Actonel is not indicated for use in pediatric patients (see *Pediatric Use [8.4]*).

Gender: Bioavailability and pharmacokinetics following oral administration are similar in men and women.

Geriatric: Bioavailability and disposition are similar in elderly (>60 years of age) and younger subjects. No dosage adjustment is necessary.

Race: Pharmacokinetic differences due to race have not been studied.

Renal Impairment: Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 mL/min.

Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min.
Hepatic Impairment: No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (<0.1% of intravenous dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.
Drug Interactions: No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (Cytochrome P450) [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week carcinogenicity study, rats were administered daily oral doses up to approximately 8 times the maximum recommended human daily dose. There were no significant drug-induced tumor findings in male or female rats. The high dose male group was terminated early in the study (Week 93) due to excessive toxicity, and data from this group were not included in the statistical evaluation of the study results. In an 80-week carcinogenicity study, mice were administered daily oral doses approximately 6.5 times the human dose. There were no significant drug-induced tumor findings in male or female mice.

Mutagenesis

Risedronate did not exhibit genetic toxicity in the following assays: *In vitro* bacterial mutagenesis in *Salmonella* and *E. coli* (Ames assay), mammalian cell mutagenesis in CHO/HGPRT assay, unscheduled DNA synthesis in rat hepatocytes and an assessment of chromosomal aberrations *in vivo* in rat bone marrow. Risedronate was positive in a chromosomal aberration assay in CHO cells at highly cytotoxic concentrations (>675 mcg/mL, survival of 6% to 7%). When the assay was repeated at doses exhibiting appropriate cell survival (29%), there was no evidence of chromosomal damage.

Impairment of Fertility

In female rats, ovulation was inhibited at an oral dose approximately 5 times the human dose. Decreased implantation was noted in female rats treated with doses approximately 2.5 times the human dose. In male rats, testicular and epididymal atrophy and inflammation were noted at approximately 13 times the human dose. Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses approximately 5 times the human dose. There was moderate-to-severe spermatid maturation block after 13 weeks in male dogs at an oral dose approximately 8 times the human dose. These findings tended to increase in severity with increased dose and exposure time.

Dosing multiples provided above are based on the recommended human dose of 30 mg/day and normalized using body surface area (mg/m^2). Actual doses were 24 mg/kg/day in rats, 32 mg/kg/day in mice, and 8, 16 and 40 mg/kg/day in dogs.

13.2 Animal Toxicology and/or Pharmacology

Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized rats and minipigs. Bone mass and biomechanical strength were increased dose-dependently at daily oral doses up to 4 and 25 times the human recommended oral dose of 5 mg for rats and minipigs, respectively. Risedronate treatment maintained the positive correlation between BMD and bone strength and did not have a negative effect on bone structure or mineralization. In intact dogs, risedronate induced positive bone balance at the level of the bone remodeling unit at oral doses ranging from 0.5 to 1.5 times the 5 mg/day human daily dose.

In dogs treated with an oral dose approximately 5 times the human daily dose, risedronate caused a delay in fracture healing of the radius. The observed delay in fracture healing is similar to other bisphosphonates. This effect did not occur at a dose approximately 0.5 times the human daily dose.

The Schenk rat assay, based on histologic examination of the epiphyses of growing rats after drug treatment, demonstrated that risedronate did not interfere with bone mineralization even at the highest dose tested, which was approximately 3500 times the lowest antiresorptive dose in this model (1.5 mcg/kg/day) and approximately 800 times the human daily dose of 5 mg. This indicates that Actonel administered at the therapeutic dose is unlikely to induce osteomalacia.

Dosing multiples provided above are based on the recommended human dose of 5 mg/day and normalized using body surface area (mg/m^2).

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

The fracture efficacy of Actonel 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in 2 large, randomized, placebo-controlled, double-blind studies that enrolled a total of almost 4000 postmenopausal women under similar protocols. The Multinational study (VERT MN) (Actonel 5 mg, N = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (VERT NA) (Actonel 5 mg, N = 821). Patients were selected on the basis of radiographic evidence of previous vertebral fracture, and therefore, had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in VERT MN, and 2.5 in VERT NA, with a broad range of baseline BMD levels. All patients in these studies received supplemental calcium 1000 mg/day. Patients with low 25-hydroxyvitamin D_3 levels (approximately 40 nmol/L or less) also received supplemental vitamin D 500 IU/day.

Effect on Vertebral Fractures

Fractures of previously undeformed vertebrae (new fractures) and worsening of pre-existing vertebral fractures were diagnosed radiographically; some of these fractures were also associated with symptoms (i.e., clinical fractures). Spinal radiographs were scheduled annually and prospectively planned analyses were based on the time to a patient's first diagnosed fracture. The primary endpoint for these studies was the incidence of new and worsening vertebral fractures across the period of 0 to 3 years. Actonel 5 mg daily significantly reduced the incidence of new and worsening vertebral fractures and of new vertebral fractures in both VERT NA and VERT MN at all time points (Table 3). The reduction in risk seen in the subgroup of patients who had 2 or more vertebral fractures at study entry was similar to that seen in the overall study population.

Table 3 The Effect of Actonel on the Risk of Vertebral Fractures

	Proportion of Patients with Fracture (%)[a]			
VERT NA	Placebo N = 678	ACTONEL 5 mg N = 696	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 - 1 Year	7.2	3.9	3.3	49
0 - 2 Years	12.8	8.0	4.8	42
0 - 3 Years	18.5	13.9	4.6	33
New				
0 - 1 Year	6.4	2.4	4.0	65
0 - 2 Years	11.7	5.8	5.9	55
0 - 3 Years	16.3	11.3	5.0	41
VERT MN	Placebo N = 346	Actonel 5 mg N = 344	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 - 1 Year	15.3	8.2	7.1	50
0 - 2 Years	28.3	13.9	14.4	56
0 - 3 Years	34.0	21.8	12.2	46
New				
0 - 1 Year	13.3	5.6	7.7	61
0 - 2 Years	24.7	11.6	13.1	59
0 - 3 Years	29.0	18.1	10.9	49

[a] Calculated by Kaplan-Meier methodology.

Effect on Osteoporosis-Related Nonvertebral Fractures

In VERT MN and VERT NA, a prospectively planned efficacy endpoint was defined consisting of all radiographically confirmed fractures of skeletal sites accepted as associated with osteoporosis. Fractures at these sites were collectively referred to as osteoporosis-related nonvertebral fractures. Actonel 5 mg daily significantly reduced the incidence of nonvertebral osteoporosis-related fractures over 3 years in VERT NA (8% versus 5%; relative risk reduction 39%) and reduced the fracture incidence in VERT MN from 16% to 11%. There was a significant reduction from 11% to 7% when the studies were combined, with a corresponding 36% reduction in relative risk. Figure 1 shows the overall results as well as the results at the individual skeletal sites for the combined studies.

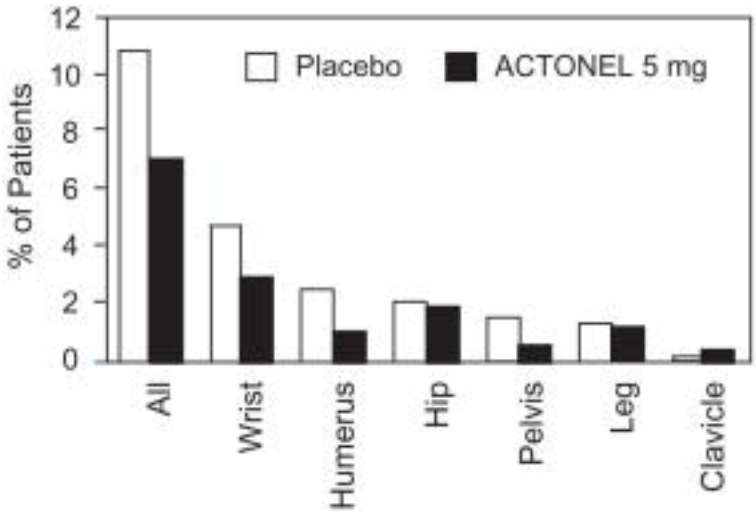


Figure 1 Nonvertebal Osteoporosis-Related Fractures Cumulative Incidence Over 3 Years Combined VERT MN and VERT NA

Effect on Bone Mineral Density

The results of 4 randomized, placebo-controlled trials in women with postmenopausal osteoporosis (VERT MN, VERT NA, BMD MN, BMD NA) demonstrate that Actonel 5 mg daily increases BMD at the spine, hip, and wrist compared to the effects seen with placebo. Table 4 displays the significant increases in BMD seen at the lumbar spine, femoral neck, femoral trochanter, and midshaft radius in these trials compared to placebo. In both VERT studies (VERT MN and VERT NA), Actonel 5 mg daily produced increases in lumbar spine BMD that were progressive over the 3 years of treatment, and were statistically significant relative to baseline and to placebo at 6 months and at all later time points.

Table 4 Mean Percent Increase in BMD from Baseline in Patients Taking Actonel 5 mg or Placebo at Endpoint[a]

	VERT MN[b]		VERT NA[b]		BMD MN[c]		BMD NA[c]	
	Placebo N = 323	5 mg N = 323	Placebo N = 599	5 mg N = 606	Placebo N = 161	5 mg N = 148	Placebo N = 191	5 mg N = 193
Lumbar Spine	1.0	6.6	0.8	5.0	0.0	4.0	0.2	4.8
Femoral Neck	-1.4	1.6	-1.0	1.4	-1.1	1.3	0.1	2.4
Femoral Trochanter	-1.9	3.9	-0.5	3.0	-0.6	2.5	1.3	4.0
Midshaft Radius	-1.5*	0.2*	-1.2*	0.1*	ND		ND	

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

[b] The duration of the studies was 3 years.

[c] The duration of the studies was 1.5 to 2 years.

* BMD of the midshaft radius was measured in a subset of centers in VERT MN (placebo, N = 222; 5 mg, N = 214) and VERT NA (placebo, N = 310; 5 mg, N = 306).

ND = analysis not done

Actonel 35 mg once-a-week (N = 485) was shown to be non-inferior to Actonel 5 mg daily (N = 480) in a 1-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 4.0% (3.7, 4.3; 95% confidence interval [CI]) in the 5 mg daily group (N = 391) and 3.9% (3.6, 4.3; 95% CI) in the 35 mg once-a-week group (N = 387) and the mean difference between 5 mg daily and 35 mg once-a-week was 0.1% (-0.4, 0.6; 95% CI). The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.

In a double-blind, multicenter study of postmenopausal women with osteoporosis, treatment with Actonel 75 mg two consecutive days per month (N = 616) was shown to be non-inferior to Actonel 5 mg daily (N = 613). In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 3.6% (3.3, 3.9; 95% CI) in the 5 mg daily group (N = 527) and

3.4% (3.1, 3.7; 95% CI) in the 75 mg two days per month group (N = 524) with a mean difference between groups being 0.2% (-0.2, 0.6; 95% CI). The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.
Actonel 150 mg once-a-month (N = 650) was shown to be non-inferior to Actonel 5 mg daily (N = 642) in a 1-year, double-blind, multicenter study of postmenopausal women with osteoporosis. The primary efficacy analysis was conducted in all randomized patients with baseline and post-baseline lumbar spine BMD values (modified intent-to-treat population) using last observation carried forward. The mean increases from baseline in lumbar spine BMD at 1 year were 3.4% (3.0, 3.8; 95% CI) in the 5 mg daily group (N = 561), and 3.5% (3.1, 3.9; 95% CI) in the 150 mg once-a-month group (N = 578) with a mean difference between groups being -0.1% (-0.5, 0.3; 95% CI). The results of the completers analysis were consistent with the primary efficacy analysis. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.

Histology/Histomorphometry

Bone biopsies from 110 postmenopausal women were obtained at endpoint. Patients had received placebo or daily Actonel (2.5 mg or 5 mg) for 2 to 3 years. Histologic evaluation (N = 103) showed no osteomalacia, impaired bone mineralization, or other adverse effects on bone in Actonel-treated women. These findings demonstrate that bone formed during Actonel administration is of normal quality. The histomorphometric parameter mineralizing surface, an index of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 21 treated with placebo and 23 patients treated with Actonel 5 mg. Mineralizing surface decreased moderately in Actonel-treated patients (median percent change: placebo, -21%; Actonel 5 mg, -74%), consistent with the known effects of treatment on bone turnover.

Effect on Height

In the two 3-year osteoporosis treatment studies, standing height was measured yearly by stadiometer. Both Actonel and placebo-treated groups lost height during the studies. Patients who received Actonel had a statistically significantly smaller loss of height than those who received placebo. In VERT MN, the median annual height change was -2.4 mm/yr in the placebo group compared to -1.3 mm/yr in the Actonel 5 mg daily group. In VERT NA, the median annual height change was -1.1 mm/yr in the placebo group compared to -0.7 mm/yr in the Actonel 5 mg daily group.

14.2 Prevention of Osteoporosis in Postmenopausal Women

The safety and effectiveness of Actonel 5 mg daily for the prevention of postmenopausal osteoporosis were demonstrated in a 2-year, double-blind, placebo-controlled study of 383 postmenopausal women (age range 42 to 63 years) within three years of menopause (Actonel 5 mg, N = 129). All patients in this study received supplemental calcium 1000 mg/day. Increases in BMD were observed as early as 3 months following initiation of Actonel treatment. Actonel 5 mg daily produced significant mean increases in BMD at the lumbar spine, femoral neck, and trochanter compared to placebo at the end of the study (Figure 2). Actonel 5 mg daily was also effective in patients with lower baseline lumbar spine BMD (more than 1 SD below the premenopausal mean) and in those with normal baseline lumbar spine BMD. Bone mineral density at the distal radius decreased in both Actonel and placebo-treated women following 1 year of treatment.

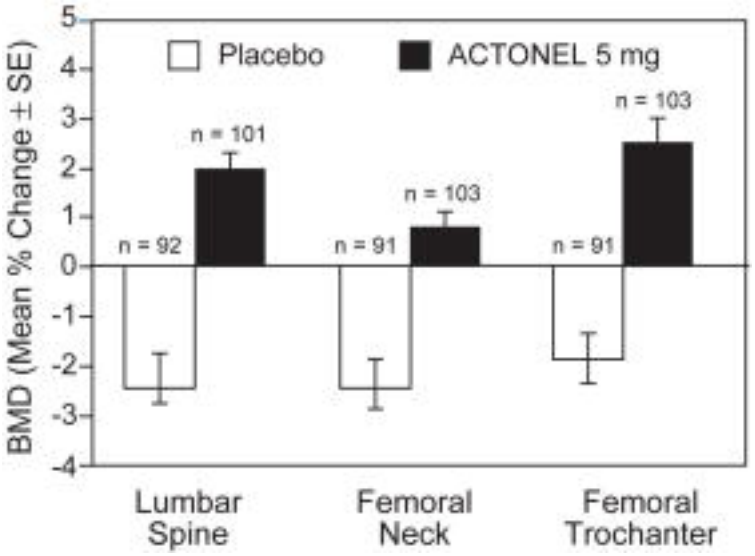


Figure 2 Change in BMD from Baseline 2-Year Prevention Study

The safety and effectiveness of Actonel 35 mg once-a-week for the prevention postmenopausal osteoporosis were demonstrated in a 1-year, double-blind, placebo-controlled study of 278 patients (Actonel 35 mg, N = 136). All patients were supplemented with 1000 mg elemental calcium and 400 IU vitamin D per day. The primary efficacy measure was the percent change in lumbar spine BMD from baseline after 1 year of treatment using LOCF (last observation carried forward). Actonel 35 mg once-a-week resulted in a statistically significant mean difference from placebo in lumbar spine BMD of +2.9% (least square mean for placebo -1.05%;

risedronate +1.83%). Actonel 35 mg once-a-week also showed a statistically significant mean difference from placebo in BMD at the total proximal femur of +1.5% (placebo -0.53%; risedronate +1.01%), femoral neck of +1.2% (placebo -1.00%; risedronate +0.22%), and trochanter of +1.8% (placebo -0.74%; risedronate +1.07%).

Combined Administration with Hormone Replacement Therapy

The effects of combining Actonel 5 mg daily with conjugated estrogen 0.625 mg daily (N = 263) were compared to the effects of conjugated estrogen alone (N = 261) in a 1-year, randomized, double-blind study of women ages 37 to 82 years, who were on average 14 years postmenopausal. The BMD results for this study are presented in Table 5.

Table 5 Percent Change from Baseline in BMD After 1 Year of Treatment

	Estrogen 0.625 mg N = 261	Actonel 5 mg + Estrogen 0.625 mg N = 263
Lumbar Spine	4.6 ± 0.20	5.2 ± 0.23
Femoral Neck	1.8 ± 0.25	2.7 ± 0.25
Femoral Trochanter	3.2 ± 0.28	3.7 ± 0.25
Midshaft Radius	0.4 ± 0.14	0.7 ± 0.17
Distal Radius	1.7 ± 0.24	1.6 ± 0.28
Values shown are mean (±SEM) percent change from baseline.		

Histology/Histomorphometry

Bone biopsies from 53 postmenopausal women were obtained at endpoint. Patients had received Actonel 5 mg plus estrogen or estrogen alone once daily for 1 year. Histologic evaluation (N = 47) demonstrated that the bone of patients treated with Actonel plus estrogen was of normal lamellar structure and normal mineralization. The histomorphometric parameter mineralizing surface, a measure of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 12 patients treated with Actonel plus estrogen and 12 treated with estrogen alone. Mineralizing surface decreased in both treatment groups (median percent change: Actonel plus estrogen, -79%; estrogen alone, -50%), consistent with the known effects of these agents on bone turnover.

14.3 Men with Osteoporosis

The effects of Actonel 35 mg once-a-week on BMD were examined in a 2-year, double-blind, placebo-controlled, multinational study in 285 men with osteoporosis (Actonel, N = 192). The patients had a mean age of 60.6 years (range 36 to 84 years) and 95% were Caucasian. At baseline, mean lumbar spine T-score was -3.2 and mean femoral neck T-score was -2.4. All patients in the study had either, 1) a BMD T-score ≤-2 at the femoral neck and ≤-1 at the lumbar spine, or 2) a BMD T-score ≤-1 at the femoral neck and ≤-2.5 at the lumbar spine. All patients were supplemented with calcium 1000 mg/day and vitamin D 400 to 500 IU/day. Actonel 35 mg once-a-week produced significant mean increases in BMD at the lumbar spine, femoral neck, trochanter, and total hip compared to placebo after 2 years of treatment (treatment difference: lumbar spine, 4.5%; femoral neck, 1.1%; trochanter, 2.2%; total proximal femur, 1.5%).

14.4 Glucocorticoid-Induced Osteoporosis

Bone Mineral Density

Two 1-year, double-blind, placebo-controlled trials in patients who were taking ≥7.5 mg/day of prednisone or equivalent demonstrated that Actonel 5 mg daily was effective in the prevention and treatment of glucocorticoid-induced osteoporosis in men and women who were either initiating or continuing glucocorticoid therapy. The efficacy of Actonel therapy for glucocorticoid-induced osteoporosis beyond one year has not been studied.

The prevention study enrolled 228 patients (Actonel 5 mg, N = 76) (18 to 85 years of age), each of whom had initiated glucocorticoid therapy (mean daily dose of prednisone 21 mg) within the previous 3 months (mean duration of use prior to study 1.8 months) for rheumatic, skin, and pulmonary diseases. The mean lumbar spine BMD was normal at baseline (average T-score -0.7). All patients in this study received supplemental calcium 500 mg/day. By the third month of treatment, and continuing through the year-long treatment, the placebo group experienced losses in BMD at the lumbar spine, femoral neck, and trochanter, while BMD was maintained or increased in the Actonel 5 mg group. At each skeletal site there were statistically significant differences between the placebo group and the Actonel 5 mg group at all timepoints (Months 3, 6, 9, and 12). The treatment differences increased with continued treatment. Although BMD increased at the distal radius in the Actonel 5 mg group compared to the placebo group, the difference was not statistically significant. The differences between placebo and Actonel 5 mg after 1 year were 3.8% at the lumbar spine, 4.1% at the femoral neck, and 4.6% at the trochanter, as shown in Figure 3. The results at these skeletal sites were similar to the overall results when the subgroups of men and postmenopausal women, but not premenopausal women, were analyzed separately. Actonel was effective at the lumbar spine, femoral neck, and trochanter regardless of age (<65 vs. ≥65), gender, prior and concomitant glucocorticoid dose, or baseline BMD. Positive treatment effects were also observed in patients taking glucocorticoids for a broad range of rheumatologic disorders, the most common of which were rheumatoid arthritis, temporal arteritis, and polymyalgia rheumatica.

The treatment study of similar design enrolled 290 patients (Actonel 5 mg, N = 100) (19 to 85 years of age) with continuing, long-term (≥6 months) use of glucocorticoids (mean duration of use prior to study 60 months; mean daily dose of prednisone 15 mg) for rheumatic, skin, and pulmonary diseases. The baseline mean lumbar spine BMD was low (1.63 SD below the young healthy population mean), with 28% of the patients more than 2.5 SD below the mean. All patients in this study received supplemental calcium 1000 mg/day and vitamin D 400 IU/day.

After 1 year of treatment, the BMD of the placebo group was within ±1% of baseline levels at the lumbar spine, femoral neck, and trochanter. Actonel 5 mg increased BMD at the lumbar spine (2.9%), femoral neck (1.8%), and trochanter (2.4%). The differences between Actonel and placebo were 2.7% at the lumbar spine, 1.9% at the femoral neck, and 1.6% at the trochanter as shown in Figure 4. The differences were statistically significant for the lumbar spine and femoral neck, but not at the femoral trochanter. Actonel was similarly effective on lumbar spine BMD regardless of age (<65 vs. ≥65), gender, or pre-study glucocorticoid dose. Positive treatment effects were also observed in patients taking glucocorticoids for a broad range of rheumatologic disorders, the most common of which were rheumatoid arthritis, temporal arteritis, and polymyalgia rheumatica.

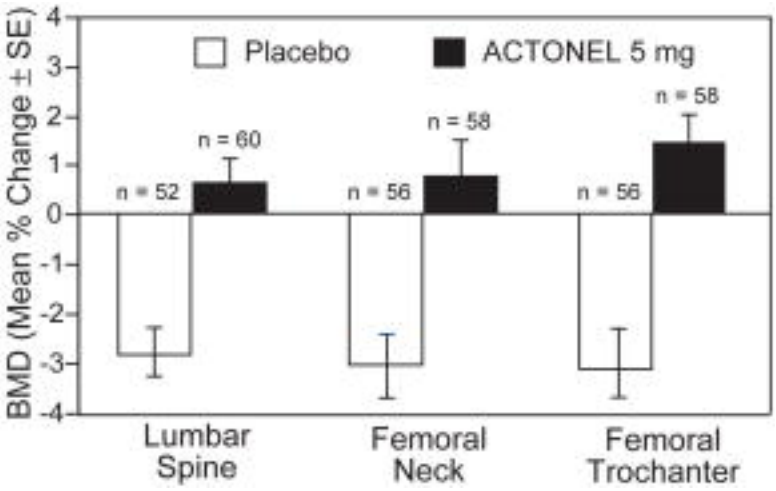


Figure 3 Change in BMD from Baseline Patients Recently Initiating Glucocorticoid Therapy

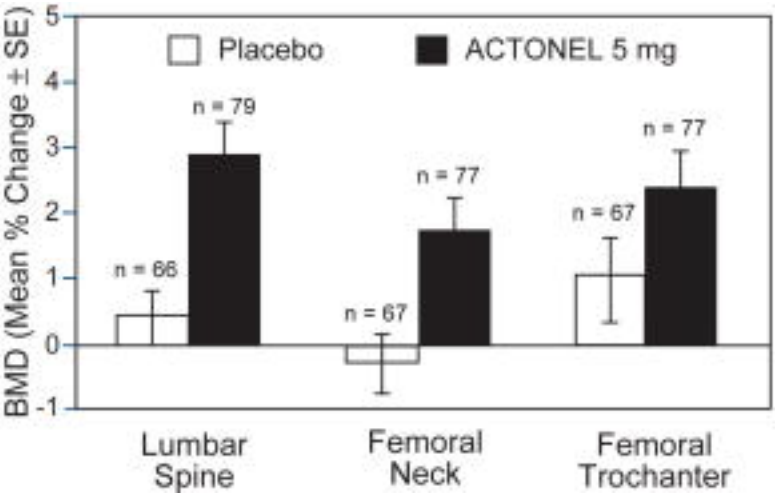


Figure 4 Change in BMD from Baseline Patients on Long-Term Glucocorticoid Therapy

Vertebral Fractures

In the prevention study of patients initiating glucocorticoids, the incidence of vertebral fractures at 1 year was reduced from 17% in the placebo group to 6% in the Actonel group. In the treatment study of patients continuing glucocorticoids, the incidence of vertebral fractures was reduced from 15% in the placebo group to 5% in the Actonel group (Figure 5). The statistically significant reduction in vertebral fracture incidence in the analysis of the combined studies corresponded to an absolute risk reduction of 11% and a relative risk reduction of 70%. All vertebral fractures were diagnosed radiographically; some of these fractures also were associated with symptoms (i.e., clinical fractures).

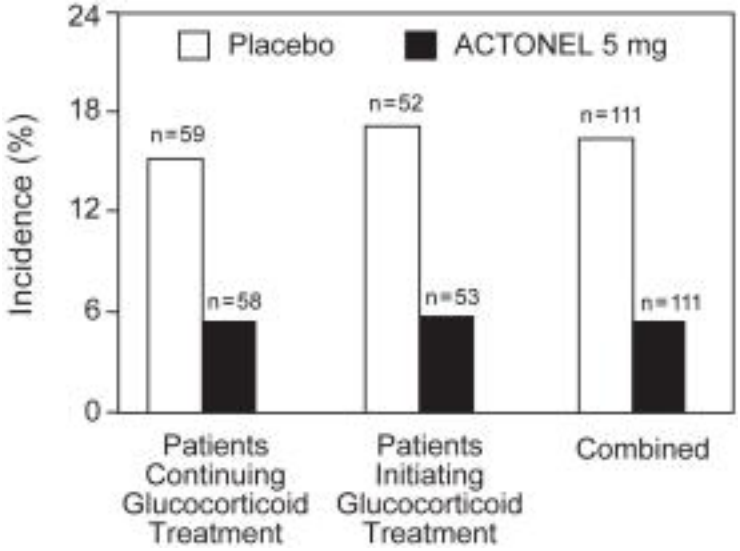


Figure 5 Incidence of Vertebral Fractures in Patients Initiating or Continuing Glucocorticoid Therapy

Histology/Histomorphometry

Bone biopsies from 40 patients on glucocorticoid therapy were obtained at endpoint. Patients had received placebo or daily Actonel (2.5 mg or 5 mg) for 1 year. Histologic evaluation (N = 33) showed that bone formed during treatment with Actonel was of normal lamellar structure and normal mineralization, with no bone or marrow abnormalities observed. The histomorphometric parameter mineralizing surface, a measure of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 10 patients treated with Actonel 5 mg. Mineralizing surface decreased 24% (median percent change) in these patients. Only a small number of placebo-treated patients had both baseline and post-treatment biopsy samples, precluding a meaningful quantitative assessment.

14.5 Treatment of Paget's Disease

The efficacy of Actonel was demonstrated in 2 clinical studies involving 120 men and 65 women. In a double-blind, active-controlled study of patients with moderate-to-severe Paget's disease (serum alkaline phosphatase levels of at least 2 times the upper limit of normal), patients were treated with Actonel 30 mg daily for 2 months or Didronel® (etidronate disodium) 400 mg daily for 6 months. At Day 180, 77% (43/56) of Actonel-treated patients achieved normalization of serum alkaline phosphatase levels, compared to 10.5% (6/57) of patients treated with Didronel ($p<0.001$). At Day 540, 16 months after discontinuation of therapy, 53% (17/32) of Actonel-treated patients and 14% (4/29) of Didronel-treated patients with available data remained in biochemical remission.

During the first 180 days of the active-controlled study, 85% (51/60) of Actonel-treated patients demonstrated a ≥75% reduction from baseline in serum alkaline phosphatase excess (difference between measured level and midpoint of the normal range) with 2 months of treatment compared to 20% (12/60) in the Didronel-treated group with 6 months of treatment ($p<0.001$). Changes in serum alkaline phosphatase excess over time (shown in Figure 6) were significant following only 30 days of treatment, with a 36% reduction in serum alkaline phosphatase excess at that time compared to only a 6% reduction seen with Didronel treatment at the same time point ($p<0.01$).

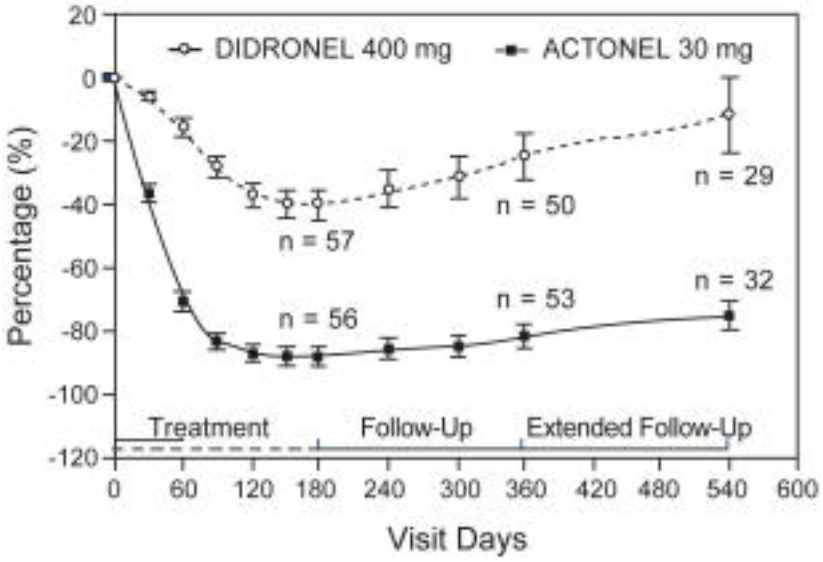


Figure 6 Mean Percent Change from Baseline in Serum Alkaline Phosphatase Excess by Visit

Response to Actonel therapy was similar in patients with mild to very severe Paget's disease. Table 6 shows the mean percent reduction from baseline at Day 180 in excess serum alkaline phosphatase in patients with mild, moderate, or severe disease.

Table 6 Mean Percent Reduction from Baseline at Day 180 in Total Serum Alkaline Phosphatase Excess by Disease Severity

	Actonel 30 mg			Didronel 400 mg		
Subgroup: Baseline Disease Severity (AP)	n	Baseline Serum AP (U/L)*	Mean % Reduction	n	Baseline Serum AP (U/L)*	Mean % Reduction
>2, <3x ULN	32	271.6 ± 5.3	-88.1	22	277.9 ± 7.45	-44.6
≥3, <7x ULN	14	475.3 ± 28.8	-87.5	25	480.5 ± 26.44	-35.0
≥7x ULN	8	1336.5 ± 134.19	-81.8	6	1331.5 ± 167.58	-47.2
*Values shown are mean ± SEM; ULN = upper limit of normal.						

Response to Actonel therapy was similar between patients who had previously received anti-pagetic therapy and those who had not. In the active-controlled study, 4 patients previously non-responsive to 1 or more courses of anti-pagetic therapy (calcitonin, Didronel) responded to treatment with Actonel 30 mg daily (defined by at least a 30% change from baseline). Each of these patients achieved at least 90% reduction from baseline in serum alkaline phosphatase excess, with 3 patients achieving normalization of serum alkaline phosphatase levels.

Histomorphometry of the bone was studied in 14 patients with bone biopsies: 9 patients had biopsies from pagetic bone lesions and 5 patients from non-pagetic bone. Bone biopsy results in non-pagetic bone did not reveal osteomalacia, impairment of bone remodeling, or induction of a significant decline in bone turnover in patients treated with Actonel.

16 HOW SUPPLIED/STORAGE AND HANDLING

Actonel® is available as follows:

5 mg film-coated, oval, yellow tablets with RSN on 1 face and 5 mg on the other.
NDC 0430-0471-15 bottle of 30

30 mg film-coated, oval, white tablets with RSN on 1 face and 30 mg on the other.
NDC 0430-0470-15 bottle of 30

35 mg film-coated, oval, orange tablets with RSN on 1 face and 35 mg on the other.
NDC 0430-0472-03 dose pack of 4
NDC 0430-0472-07 dose pack of 12

75 mg film-coated, oval, pink tablets with RSN on 1 face and 75 mg on the other.
NDC 0430-0477-02 dose pack of 2

150 mg film-coated, oval, blue tablets with RSN on 1 face and 150 mg on the other.
NDC 0430-0478-01 dose pack of 1
NDC 0430-0478-02 dose pack of 3

Store at controlled room temperature 20° to 25° C (68° to 77° F) [*see* USP].

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.1)]

The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions. Specifically, Actonel should be taken at least 30 minutes before the first food or drink of the day other than water.

To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, patients should take Actonel while in an upright position (sitting or standing) with a full glass of plain water (6 to 8 oz). Patients should not lie down for 30 minutes after taking the medication [*see Warnings and Precautions (5.1)*]. Patients should not chew or suck on the tablet because of a potential for oropharyngeal irritation.

Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or severe persistent or worsening heartburn) they should consult their physician before continuing Actonel.

Patients should be instructed that if they miss a dose of Actonel 35 mg once a week, they should take 1 tablet on the morning after they remember and return to taking 1 tablet once a week, as originally scheduled on their chosen day. Patients should not take 2 tablets on the same day.

If one or both tablets of Actonel 75 mg on two consecutive days per month are missed, and the next month's scheduled doses are more than 7 days away, the patient should be instructed as follows:

- If both tablets are missed, take one Actonel 75 mg tablet in the morning after the day it is remembered and then the other tablet on the next consecutive morning.

- If only one Actonel 75 mg tablet is missed, take the missed tablet in the morning after the day it is remembered.

Patients should then return to taking their Actonel 75 mg on two consecutive days per month as originally scheduled. Patients should not take more than two 75 mg tablets within 7 days.

If one or both tablets of Actonel 75 mg on two consecutive days per month are missed, and the next month's scheduled doses are within 7 days, patients should wait until their next month's scheduled doses and then continue taking Actonel 75 mg on two consecutive days per month as originally scheduled.

If the dose of Actonel 150 mg once-a-month is missed, and the next month's scheduled dose is more than 7 days away, the patient should be instructed to take the missed tablet in the morning after the day it is remembered. Patients should then return to taking their Actonel 150 mg once-a-month as originally scheduled. Patients should not take more than one 150 mg tablet within 7 days.

If the dose of Actonel 150 mg once-a-month is missed, and the next month's scheduled dose is within 7 days, patients should wait until their next month's scheduled dose and then continue taking Actonel 150 mg once-a-month as originally scheduled.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate [*see Warnings and Precautions (5.2)*]. Calcium supplements or calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of Actonel and should be taken at a different time of the day, as with food.

Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as excessive cigarette smoking, and/or alcohol consumption, if these factors exist.

Physicians should instruct their patients to read the Patient Information before starting therapy with Actonel 5 mg, 35 mg, 75 mg, or 150 mg and to re-read it each time the prescription is renewed.

Patients should be reminded to give all of their healthcare providers an accurate medication history. Instruct patients to tell all of their healthcare providers that they are taking Actonel. Patients should be instructed that any time they have a medical problem they think may be from Actonel, they should talk to their doctor.

MEDICATION GUIDE

Medication Guide

Actonel® (AK-toh-nel)
(*risedronate sodium*)
Tablets

Read the Medication Guide that comes with Actonel® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. Talk to your doctor if you have any questions about Actonel.

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

Actonel can cause serious side effects including:

1. Esophagus problems

2. Low calcium levels in your blood (hypocalcemia)

3. Severe jaw bone problems (osteonecrosis)

4. Bone, joint, or muscle pain

5. Unusual thigh bone fractures

1. Esophagus problems.
Some people who take Actonel may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

- **It is important that you take Actonel exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take Actonel?")**

- **Stop taking Actonel and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.**

2. Low calcium levels in your blood (hypocalcemia).
Actonel may lower the calcium levels in your blood. If you have low blood calcium before you start taking Actonel, it may get worse during treatment. Your low blood calcium must be treated before you take Actonel. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles

- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take Actonel. Take calcium and vitamin D as your doctor tells you to.

3. Severe jaw bone problems (osteonecrosis).
Severe jaw bone problems may happen when you take Actonel. Your doctor should examine your mouth before you start Actonel. Your doctor may tell you to see your dentist before you start Actonel. It is important for you to practice good mouth care during treatment with Actonel.

4. Bone, joint, or muscle pain.
Some people who take Actonel develop severe bone, joint, or muscle pain.

5. Unusual thigh bone fractures.
Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is Actonel?
Actonel is a prescription medicine used to:

- Treat or prevent osteoporosis in women after menopause. Actonel helps increase bone mass and helps reduce the chance of having a spinal or non-spinal fracture (break).

- Increase bone mass in men with osteoporosis.

- Treat or prevent osteoporosis in either men or women who are taking corticosteroid medicines.

- Treat certain men and women who have Paget's disease of the bone.

It is not known how long Actonel works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if Actonel is still right for you.
Actonel is not for use in children.

Who should not take Actonel?
Do not take Actonel if you:

- Have certain problems with your esophagus, the tube that connects your mouth with your stomach

- Cannot stand or sit upright for at least 30 minutes

- Have low levels of calcium in your blood

- Are allergic to Actonel any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking Actonel?
Before you start Actonel, be sure to talk to your doctor if you:

- Have problems with swallowing

- Have stomach or digestive problems

- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant, or plan to become pregnant. It is not known if Actonel can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if Actonel passes into your milk and may harm your baby.

Especially tell your doctor if you take:
- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Certain medicines may affect how Actonel works.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.
How should I take Actonel?
- Take Actonel exactly as your doctor tells you. Your doctor may change your dose of Actonel if needed.
- **Actonel works only if taken on an empty stomach.**
- Take 1 Actonel tablet, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take Actonel while you are sitting or standing.
- **Do not chew or suck on a tablet of Actonel**.
- Swallow Actonel tablet with a full glass (6 to 8 oz) of plain water only.
- Do **not** take Actonel with mineral water, coffee, tea, soda, or juice.

After swallowing Actonel tablet, wait at least 30 minutes:
- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take your first food or drink except for plain water.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take Actonel and after you eat your first food of the day.
If you miss a dose of Actonel, **do not** take it later in the day. Take your missed dose the next morning and then return to your normal schedule. Do not take 2 doses at the same time.
If you miss more than 2 doses of Actonel in a month, call your doctor for instructions.
If you take too much Actonel, call your doctor. Do not try to vomit. Do not lie down.
What are the possible side effects of Actonel?
Actonel may cause serious side effects**:**
- See **"What is the most important information I should know about Actonel?"**

The most common side effects of Actonel are:
- pain, including back and joint pain
- stomach area (abdominal) pain
- heartburn

You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of Actonel. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Actonel?

- Store Actonel at room temperature, 68° F to 77° F (20° C to 25° C).

Safely throw away medicine that is out of date or no longer needed.

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

General information about the safe and effective use of Actonel.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Actonel for a condition for which it was not prescribed. Do not give Actonel to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about Actonel. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Actonel that is written for health professionals.

For more information, go to www.actonel.com or call 1-800-521-8813.

What are the ingredients in Actonel?

Active ingredient: risedronate sodium

Inactive ingredients in all dose strengths: crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

Inactive ingredients specific to a dose strength: 5 mg—ferric oxide yellow, lactose monohydrate; 30 mg—lactose monohydrate; 35 mg—ferric oxide red, ferric oxide yellow, lactose monohydrate; 75 mg—ferric oxide red; 150 mg—FD&C blue #2 aluminum lake.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Covered under one or more of U.S. Patent Nos. 5,583,122; 5,994,329; 6,015,801; 6,096,342; 6,165,513; 6,410,520; 6,432,932; 6,465,443; and 6,562,974.

Manufactured by:
Warner Chilcott Puerto Rico LLC,
Manati, Puerto Rico 00674
or
Norwich Pharmaceuticals, Inc.,
North Norwich, NY 13814
or
Chinoin Pharmaceutical and Chemical Works Private Co. Ltd
Veresegyhaz, Hungary
Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813
0472G125

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 5 MG LABEL

Dispense the enclosed Medication Guide to each patient

Actonel®
(risedronate sodium) tablets
5 mg
30 Tablets
0471G051

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BONIVA Tablets safely and effectively. See full prescribing information for BONIVA Tablets.

BONIVA® (ibandronate sodium) Tablets
Initial U.S. Approval: 2003

RECENT MAJOR CHANGES

Indications and Usage (1.2)	01/2011
Warnings and Precautions (5.5)	01/2011

INDICATIONS AND USAGE

BONIVA is a bisphosphonate indicated for the treatment and prevention of postmenopausal osteoporosis. (1.1).
The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

DOSAGE AND ADMINISTRATION

One 150 mg tablet taken once monthly or one 2.5 mg tablet taken once daily (2.1)
Dosing instructions (2.2)

- Swallow whole tablet with 6-8 oz of plain water only, at least 60 minutes before the first food, beverage, or medication of the day.
- Do not lie down for at least 60 minutes after taking BONIVA.
- Do not eat, drink (except for water), or take other medication for 60 minutes after taking BONIVA.

DOSAGE FORMS AND STRENGTHS

Tablets: 2.5 mg, 150 mg (3)

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia (4, 5.1)
- Inability to stand or sit upright for at least 60 minutes (4, 5.1)
- Hypocalcemia (4)
- Hypersensitivity to BONIVA (4)

WARNINGS AND PRECAUTIONS

- Severe irritation of the upper gastrointestinal (GI) mucosa can occur. Dosing instructions should be followed and caution should be used in patients with active upper GI disease. Discontinue use if new or worsening symptoms occur. (5.1)
- Hypocalcemia may worsen during treatment. Correct hypocalcemia before use. (5.2)
- Severe bone, joint, and muscle pain may occur. Consider discontinuing use if symptoms develop. (5.3)
- Osteonecrosis of the jaw has been reported. (5.4)
- Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (>5%) are back pain, dyspepsia, pain in extremity, diarrhea, headache, and myalgia. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Calcium supplements, antacids and some oral medications may interfere with absorption of ibandronate. (7.1)
- Use caution when co-prescribing aspirin/nonsteroidal anti-inflammatory drugs that may worsen gastrointestinal irritation. (7.2)

USE IN SPECIFIC POPULATIONS

BONIVA is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min). (5.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 01/2011

FULL PRESCRIBING INFORMATION: CONTENTS *

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2.2 Dosing Instructions
2.3 Recommendations for Calcium and Vitamin D Supplementation
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment and Prevention of Postmenopausal Osteoporosis

BONIVA is indicated for the treatment and prevention of osteoporosis in postmenopausal women. BONIVA increases bone mineral density (BMD) and reduces the incidence of vertebral fractures.

1.2 Important Limitations of Use

The safety and effectiveness of BONIVA for the treatment of osteoporosis are based on clinical data of three years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

2 DOSAGE AND ADMINISTRATION

2.1 Dose

The dose of BONIVA is either one 150 mg tablet taken once monthly on the same date each month or one 2.5 mg tablet taken once daily.

2.2 Dosing Instructions

- 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 before taking any oral medication or supplementation, including calcium, antacids, or vitamins *(see DRUG INTERACTIONS [7.1])*.

- 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 WARNINGS AND PRECAUTIONS [5.1])*.

- Patients should not eat, drink anything except water, or take other medications for at least 60 minutes after taking BONIVA.

- Plain water is the only drink that should be taken with BONIVA. 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.

- The BONIVA 150 mg tablet should be taken on the same date each month (i.e., the patient's BONIVA day).

- The patient must not take two 150 mg tablets within the same week.

- If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150 mg tablet in the morning following the date that it is remembered. The patient should then return to taking one BONIVA 150 mg tablet every month in the morning of their chosen day, according to their original schedule.

- If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until the subsequent month's scheduled BONIVA day to take their tablet. The patient should then return to taking one BONIVA 150 mg tablet every month in the morning of their chosen day, according to their original schedule.

2.3 Recommendations for Calcium and Vitamin D Supplementation
Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate *(see DRUG INTERACTIONS [7.1])*.

2.4 Use in Specific Populations
BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance of <30 mL/min).
No dose adjustment is necessary for patients with mild or moderate renal impairment.
No dose adjustment is necessary for the elderly, or for patients with hepatic impairment.

3 DOSAGE FORMS AND STRENGTHS
Tablets, 2.5 mg and 150 mg

4 CONTRAINDICATIONS
- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia *(see Upper Gastrointestinal Adverse Reactions [5.1])*

- Inability to stand or sit upright for at least 60 minutes *(see Dosing Instructions [2.2], Upper Gastrointestinal Adverse Reactions [5.1])*

- Hypocalcemia *(see WARNINGS AND PRECAUTIONS [5.2])*

- Known hypersensitivity to BONIVA or to any of its excipients *(see ADVERSE REACTIONS [6.2]).*

5 WARNINGS AND PRECAUTIONS

5.1 Upper Gastrointestinal Adverse Reactions
BONIVA, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when BONIVA is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers).
Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. In some cases, these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue BONIVA and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.
The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates and/or who fail to swallow it with the recommended full glass (6-8 oz) of water, and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient *(see DOSAGE AND ADMINISTRATION [2.2])*. In patients who cannot comply with dosing instructions due to mental disability, therapy with BONIVA should be used under appropriate supervision.
There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

5.2 Hypocalcemia and Mineral Metabolism
Treat hypocalcemia and other disturbances of bone and mineral metabolism before starting BONIVA therapy. Adequate intake of calcium and vitamin D is important in all patients to prevent hypocalcemia *(see DOSAGE AND ADMINISTRATION [2.3])*. Hypocalcemia following dosing has been reported postmarketing.

5.3 Musculoskeletal Pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking BONIVA and other bisphosphonates *(see ADVERSE REACTIONS [6])*. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

5.4 Jaw Osteonecrosis

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (e.g., anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally *(see ADVERSE REACTIONS [6.2])*.

For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low-trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.6 Severe Renal Impairment

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment and Prevention of Postmenopausal Osteoporosis

Daily Dosing

The safety of BONIVA 2.5 mg once daily in the treatment and prevention of postmenopausal osteoporosis was assessed in 3577 patients aged 41 – 82 years. The duration of the trials was 2 to 3 years, with 1134 patients exposed to placebo and 1140 exposed to BONIVA 2.5 mg. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors and H2 antagonists were included in these clinical trials. All patients received 500 mg calcium plus 400 IU vitamin D supplementation daily.

The incidence of all-cause mortality was 1% in the placebo group and 1.2% in the BONIVA 2.5 mg daily group. 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 daily group and the placebo group. *Table 1* lists adverse events from the treatment and prevention studies reported in ≥2% of patients and more frequently in patients treated daily with BONIVA than patients treated with placebo.

Table 1 Adverse Events Occurring at a Frequency ≥2% and More Frequently in Patients Treated with BONIVA than in Patients Treated with Placebo Daily in the Osteoporosis Treatment and Prevention Studies

Body System	**Placebo % (n=1134)**	**BONIVA 2.5 mg % (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

Gastrointestinal Adverse Events

The incidence of adverse events in the placebo and BONIVA 2.5 mg daily groups were: dyspepsia (10% vs. 12%), diarrhea (5% vs. 7%), and abdominal pain (5% vs. 6%).

Musculoskeletal Adverse Events

The incidence of adverse events in the placebo and BONIVA 2.5 mg daily groups were: back pain (12% vs. 14%), arthralgia (14% vs. 14%) and myalgia (5% vs. 6%).

Ocular Adverse Events

Reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as iritis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued. There were no reports of ocular inflammation in studies with BONIVA 2.5 mg daily.

Monthly Dosing

The safety of BONIVA 150 mg once monthly in the treatment of postmenopausal osteoporosis was assessed in a two year trial which enrolled 1583 patients aged 54 – 81 years, with 395 patients exposed to BONIVA 2.5 mg daily and 396 exposed to BONIVA 150 mg monthly. Patients with active or significant pre-existing gastrointestinal disease were excluded from this trial. Patients with dyspepsia or concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors and H2 antagonists were included in this study. All patients received 500 mg calcium plus 400 IU vitamin D supplementation daily.

After one year, the incidence of all-cause mortality was 0.3% in both the BONIVA 2.5 mg daily group and the BONIVA 150 mg monthly group. The incidence of serious adverse events was 5% in the BONIVA 2.5 mg daily group and 7% in the BONIVA 150 mg monthly group. The percentage of patients who withdrew from treatment due to adverse events was 9% in the BONIVA 2.5 mg daily group and 8% in the BONIVA 150 mg monthly group. *Table 2* lists the adverse events reported in ≥2% of patients.

Table 2 Adverse Events with an Incidence of at Least 2% in Patients Treated with BONIVA 2.5 mg Daily or 150 mg Once-Monthly for Treatment of Postmenopausal Osteoporosis

Body System/Adverse Event	BONIVA 2.5 mg Daily % (n=395)	BONIVA 150 mg Monthly % (n=396)
Vascular Disorders		
Hypertension	7.3	6.3
Gastrointestinal Disorders		
Dyspepsia	7.1	5.6
Nausea	4.8	5.1
Diarrhea	4.1	5.1
Constipation	2.5	4.0
Abdominal Pain*	5.3	7.8
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3.5	5.6
Back Pain	4.3	4.5
Pain in Extremity	1.3	4.0
Localized Osteoarthritis	1.3	3.0
Myalgia	0.8	2.0
Muscle Cramp	2.0	1.8
Infections and Infestations		
Influenza	3.8	4.0
Nasopharyngitis	4.3	3.5
Bronchitis	3.5	2.5
Urinary Tract Infection	1.8	2.3
Upper Respiratory Tract Infection	2.0	2.0
Nervous System Disorders		
Headache	4.1	3.3
Dizziness	1.0	2.3
General Disorders and Administration Site Conditions		
Influenza-like Illness†	0.8	3.3
Skin and Subcutaneous Tissue Disorders		
Rash‡	1.3	2.3
Psychiatric Disorders		
Insomnia	0.8	2.0

*Combination of abdominal pain and abdominal pain upper
†Combination of influenza-like illness and acute phase reaction
‡Combination of rash pruritic, rash macular, rash papular, rash generalized, rash erythematous, dermatitis, dermatitis allergic, dermatitis medicamentosa, erythema and exanthem

Gastrointestinal Adverse Events

The incidence of adverse events in the BONIVA 2.5 mg daily and BONIVA 150 mg monthly groups were: dyspepsia (7% vs. 6%), diarrhea (4% vs. 5%), and abdominal pain (5% vs. 8%).

Musculoskeletal Adverse Events

The incidence of adverse events in the BONIVA 2.5 mg daily and BONIVA 150 mg monthly groups were: back pain (4% vs. 5%), arthralgia (4% vs. 6%) and myalgia (1% vs. 2%).

Acute Phase Reactions

Symptoms consistent with acute phase reactions have been reported with bisphosphonate use. Over the two years of the study, the overall incidence of acute phase reaction symptoms was 3% in the BONIVA 2.5 mg daily group and 9% in the BONIVA 150 mg monthly group. These incidence rates are based on the reporting of any of 33 acute-phase reaction like symptoms within 3 days of the monthly dosing and lasting 7 days or less. Influenza like illness was reported in no patients in the BONIVA 2.5 mg daily group and 2% in the BONIVA 150 mg monthly group.

Ocular Adverse Events

Two patients who received BONIVA 150 mg once-monthly experienced ocular inflammation, one was a case of uveitis and the other scleritis.

One hundred sixty (160) postmenopausal women without osteoporosis participated in a 1-year, double-blind, placebo-controlled study of BONIVA 150 mg once-monthly for prevention of bone loss. Seventy-seven subjects received BONIVA and 83 subjects received placebo. The overall pattern of adverse events was similar to that previously observed.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of BONIVA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity

Allergic reactions including anaphylaxis, angioedema, bronchospasm and rash have been reported (*see CONTRAINDICATIONS [4]*).

Hypocalcemia

Hypocalcemia has been reported in patients treated with BONIVA (*see WARNINGS AND PRECAUTIONS [5.2]).*

Musculoskeletal Pain

Bone, joint, or muscle pain (musculoskeletal pain), described as severe or incapacitating, has been reported (*see WARNINGS AND PRECAUTIONS [5.3]*).

Jaw Osteonecrosis

Osteonecrosis of the jaw has been reported in patients treated with BONIVA (*see WARNINGS AND PRECAUTIONS [5.4]*).

7 DRUG INTERACTIONS

7.1 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, including medications containing multivalent cations (such as antacids, supplements or vitamins). Also, patients should wait at least 60 minutes after dosing before taking any other oral medications *(see PATIENT COUNSELING INFORMATION [17.1]).*

7.2 Aspirin/Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Because aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with BONIVA.

7.3 H2 Blockers

In healthy volunteers, co-administration with ranitidine resulted in a 20% increased bioavailability of ibandronate, which was not considered to be clinically relevant *(see CLINICAL PHARMACOLOGY [12.3])*.

7.4 Drug/Laboratory Test Interactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category C

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.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic

circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

In female rats given ibandronate orally at doses ≥3 times human exposure at the recommended daily oral dose of 2.5 mg or ≥1 times human exposure at the recommended once-monthly oral dose of 150 mg beginning 14 days before mating and continuing through lactation, maternal deaths were observed at the time of delivery in all dose groups. Perinatal pup loss in dams given 45 times human exposure at the recommended daily dose and 13 times the recommended once-monthly dose was likely related to maternal dystocia. Calcium supplementation did not completely prevent dystocia and periparturient mortality in any of the treated groups at ≥16 times the recommended daily dose and ≥4.6 times the recommended once-monthly dose. 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 from gestation day 17 through lactation day 21 (following closure of the hard palate through weaning), maternal toxicity, including dystocia and mortality, fetal perinatal and postnatal mortality, were observed at doses equivalent to human exposure at the recommended daily and ≥4 times the recommended once-monthly dose. 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 *(see NONCLINICAL TOXICOLOGY [13.2])*.

Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at oral doses 30 times the human exposure at the recommended daily oral dose of 2.5 mg and ≥9 times the recommended once-monthly oral dose of 150 mg. Impaired pup neuromuscular development (cliff avoidance test) was observed at 45 times human exposure at the daily dose and 13 times the once-monthly dose *(see NONCLINICAL TOXICOLOGY [13.2])*.

In pregnant rabbits treated orally with ibandronate during gestation at doses ≥8 times the recommended human daily oral dose of 2.5 mg and ≥4 times the recommended human once-monthly oral dose of 150 mg, dose-related maternal mortality was observed in all treatment groups. The deaths occurred prior to parturition and were associated with lung edema and hemorrhage. No significant fetal anomalies were observed *(see NONCLINICAL TOXICOLOGY [13.2])*.

8.3 Nursing Mothers

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. In lactating rats treated with intravenous doses, ibandronate was present in breast milk from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the patients receiving BONIVA 2.5 mg daily in postmenopausal osteoporosis studies, 52% were over 65 years of age, and 10% were over 75 years of age. Of the patients receiving BONIVA 150 mg once-monthly in the postmenopausal osteoporosis 1-year study, 52% were over 65 years of age, and 9% 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.

8.6 Renal Impairment

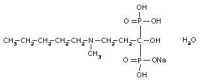
BONIVA is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min).

10 OVERDOSAGE

No specific information is available on the treatment of overdosage of 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.

11 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 daily oral administration or as a white, oblong, 150 mg film-coated tablet for once-monthly oral administration. One 2.5 mg film-coated tablet contains 2.813 mg ibandronate monosodium monohydrate, equivalent to 2.5 mg free acid. One 150 mg film-coated tablet contains 168.75 mg ibandronate monosodium monohydrate, equivalent to 150 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.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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 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 mg to 5 mg and once-monthly doses from 100 mg to 150 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 I 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.

In a 1-year, study comparing once-monthly vs. once-daily oral dosing regimens, the median decrease from baseline in serum CTX values was -76% for patients treated with the 150 mg once-monthly regimen and -67% for patients treated with the 2.5 mg daily regimen. In a 1-year, prevention study comparing BONIVA 150 mg once-monthly to placebo, the median placebo-subtracted decrease in sCTX was -49.8%.

12.3 Pharmacokinetics

Absorption

The absorption of oral ibandronate occurs in the upper gastrointestinal tract. Plasma concentrations increase in a dose-linear manner up to 50 mg oral intake and increases nonlinearly above this dose.

Following oral dosing, 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 concomitantly 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

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. 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 plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution into bone accounts for a rapid and early decline in plasma concentrations, reaching 10% of the C_{max} within 3 or 8 hours after intravenous or oral administration, respectively. This is followed by a slower clearance phase as ibandronate redistributes back into the blood from bone. The observed apparent terminal half-life for ibandronate is generally dependent on the dose studied and on assay sensitivity. The observed apparent terminal half-life for the 150 mg ibandronate tablet upon oral administration to healthy postmenopausal women ranges from 37 to 157 hours.

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.

Specific Populations

Pediatrics

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

Geriatric

Because 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.

Gender

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

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 [2.4])*.

Hepatic Impairment

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

Drug Interactions

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

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.

13 NONCLINICAL TOXICOLOGY

13.1 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 male and female Wistar rats (systemic exposures up to 12 and 7 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg, and cumulative exposures up to 3.5 and 2 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, 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 male and female NMRI mice (exposures up to 475 and 70 times, respectively, human exposure at the recommended daily oral dose of 2.5 mg and cumulative exposures up to 135 and 20 times, respectively, human exposure at the recommended once-monthly oral dose of 150 mg, 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 (cumulative monthly exposures in males and females up to 70 and 115 times, respectively, human exposure at the recommended dose of 150 mg, based on AUC comparison). 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 daily oral dose of 2.5 mg and 115 times human exposure at the recommended once-monthly oral dose of 150 mg, 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 daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison).

13.2 Animal Reproductive and Developmental Toxicology

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 daily oral dose of 2.5 mg or ≥1 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). Perinatal pup loss in dams given 16 mg/kg/day (45 times human exposure at the recommended daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, 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 daily oral dose of 2.5 mg and ≥4.6 times human exposure at the recommended once-monthly oral dose of 150 mg, 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, fetal perinatal and postnatal mortality, were observed at doses ≥5 mg/kg/day (equivalent to human exposure at the recommended daily oral dose of 2.5 mg and ≥4 times human exposure at the recommended once-monthly oral dose of 150 mg, 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 daily oral dose of 2.5 mg and ≥9 times human exposure at the recommended once-monthly oral dose of 150 mg, 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 daily oral dose of 2.5 mg and 13 times human exposure at the recommended once-monthly oral dose of 150 mg, 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 daily oral dose of 2.5 mg and ≥4 times the recommended human once-monthly oral dose of 150 mg, 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.

13.3 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 once-monthly intermittent administration of ibandronate to ovariectomized rats or monkeys was associated with suppression of bone turnover and increases in bone mass. In both rats and monkeys, vertebral BMD, trabecular density, and biomechanical strength were increased dose-dependently at doses up to 15 times the recommended human daily oral dose of 2.5 mg, or cumulative monthly doses up to 8 times (rat) or 6 times (monkey) the recommended human once-monthly oral dose of 150 mg, based on body surface area (mg/m^2) or AUC comparison. In monkeys, 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.

14 CLINICAL STUDIES

14.1 Treatment of Postmenopausal Osteoporosis
Daily Dosing

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 postmenopause, 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 1 to 4 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.

Effect on Fracture Incidence

BONIVA 2.5 mg daily significantly reduced the incidence of new vertebral (primary efficacy measure) 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 3)*.

Table 3 Effect of BONIVA on the Incidence of Vertebral Fracture in the 3-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 postbaseline value prior to the study's last time point is used.
†p=0.0003 vs. placebo

BONIVA 2.5 mg daily did not reduce the incidence of nonvertebral fractures (secondary efficacy measure). There was a similar number of nonvertebral osteoporotic fractures at 3 years reported in women treated with BONIVA 2.5 mg daily [9.1%, (95% CI: 7.1%, 11.1%)] and placebo [8.2%, (95% CI: 6.3%, 10.2%)]. The two treatment groups were also similar with regard to the number of fractures reported at the individual nonvertebral sites: pelvis, femur, wrist, forearm, rib, and hip.

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 daily 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 time points. 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 4* displays the significant increases in BMD seen at the lumbar spine, total hip, femoral neck, and trochanter compared to placebo.

Table 4 Mean Percent Change in BMD from Baseline to Endpoint in Patients Treated Daily with BONIVA 2.5 mg or Placebo in the 3-Year Osteoporosis Treatment Study*

	Placebo	**BONIVA 2.5 mg Daily**
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 postbaseline 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.

Once-Monthly Dosing

The effectiveness and safety of BONIVA once-monthly were demonstrated in a randomized, double-blind, multinational, noninferiority trial in 1602 women aged 54 to 81 years, who were on average 18 years postmenopause, and had L2-L4 lumbar spine BMD T-score below -2.5 SD at baseline. The main outcome measure was the comparison of the percentage change from baseline in lumbar spine BMD after 1 year of treatment with once-monthly ibandronate (100 mg, 150 mg) to daily ibandronate (2.5 mg). All patients received 400 IU vitamin D and 500 mg calcium supplementation per day.

BONIVA 150 mg once-monthly (n=327) was shown to be noninferior to BONIVA 2.5 mg daily (n=318) in lumbar spine BMD in a 1-year, double-blind, multicenter study of women with postmenopausal osteoporosis. In the primary efficacy analysis (per-protocol population), the mean increases from baseline in lumbar spine BMD at 1 year were 3.86% (95% CI: 3.40%, 4.32%) in the 2.5 mg daily group and 4.85% (95% CI: 4.41%, 5.29%) in the 150 mg once-monthly group; the mean difference between 2.5 mg daily and 150 mg once-monthly was 0.99% (95% CI: 0.38%, 1.60%), which was statistically significant (p=0.002). The results of the intent-to-treat analysis were consistent with the primary efficacy analysis. The 150 mg once-monthly group also had consistently higher BMD increases at the other skeletal sites compared to the 2.5 mg daily group.

14.2 Prevention of Postmenopausal Osteoporosis
Daily Dosing

The safety and effectiveness of BONIVA 2.5 mg daily for the prevention of postmenopausal osteoporosis were demonstrated 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 postmenopause, 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. Increases in BMD were seen at 6 months and at all later time points. 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 to 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%.

Once-Monthly Dosing

The safety and effectiveness of BONIVA 150 mg once-monthly for the prevention of postmenopausal osteoporosis were demonstrated in a randomized, double-blind, placebo-controlled 1-year study (Monthly Prevention Study) of 160 postmenopausal women with low bone mass at baseline (T-score of -1 to -2.5). Women, aged 46 to 60 years, were on average 5.4 years postmenopause. All women received 400 IU of vitamin D and 500 mg calcium supplementation daily.

The primary efficacy measure was the relative change in BMD at the lumbar spine after 1 year of treatment. BONIVA 150 mg once-monthly resulted in a mean increase in lumbar spine BMD of 4.12% (95% confidence interval 2.96 – 5.28) compared with placebo following 1 year of treatment ($p<0.0001$), based on a 3.73% and -0.39% mean change in BMD from baseline in the 150 mg once-monthly BONIVA and placebo treatment groups, respectively. BMD at other skeletal sites was also increased relative to baseline values.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BONIVA 2.5 mg tablets: supplied as white, oblong, film-coated tablets, engraved with "IT" on one side and "L3" on the other side and packaged in bottles of 30 tablets (NDC 0004-0185-23).
BONIVA 150 mg tablets: supplied as white, oblong, film-coated tablets, engraved with "BNVA" on one side and "150" on the other side. Packaged in boxes of 3 blister packs containing 1 tablet each (NDC 0004-0186-82).

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

See FDA-APPROVED MEDICATION GUIDE (17.2)

17.1 Information for Patients

Patients should be instructed to read the Medication Guide carefully before taking BONIVA and to re-read it each time the prescription is renewed because it contains important information the patient should know about BONIVA. The Medication Guide also includes 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 taking any oral medication or supplementation including calcium, antacids or vitamins *(see DRUG INTERACTIONS [7.1])*.
- 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.
- Patients should not eat, drink anything except for water, or take other medications for 60 minutes after taking BONIVA.
- Plain water is the only drink that should be taken with BONIVA. 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.
- The BONIVA 2.5 mg tablet should be taken at the same time each day.
- If a once-daily dose is missed, the patient should be instructed to skip that dose and return to their normal schedule the next day.
- The patient must not take two 2.5 mg tablets within the same day.
- The BONIVA 150 mg tablet should be taken on the same date each month (i.e., the patient's BONIVA day).
- The patient must not take two 150 mg tablets within the same week.
- If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is more than 7 days away, the patient should be instructed to take one BONIVA 150 mg tablet in the morning following the date that it is remembered *(see DOSAGE AND ADMINISTRATION [2.3])*. The patient should then return to taking one BONIVA 150 mg tablet every month in the morning of their chosen day, according to their original schedule.

- If the once-monthly dose is missed, and the patient's next scheduled BONIVA day is only 1 to 7 days away, the patient must wait until the subsequent month's scheduled BONIVA day to take their tablet. The patient should then return to taking one BONIVA 150 mg tablet every month in the morning of their chosen day, according to their original schedule.

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.

17.2 FDA-Approved Medication Guide
Read the Medication Guide that comes with BONIVA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. Talk to your doctor if you have any questions about BONIVA.
What is the most important information I should know about BONIVA?
BONIVA can cause serious side effects including:
1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Bone, joint or muscle pain
4. Severe jaw bone problems (osteonecrosis)
5. Unusual thigh bone fractures

1. **Esophagus problems.**
   Some people who take BONIVA may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

- **It is important that you take BONIVA exactly as prescribed to help lower your chance of getting esophagus problems (see the section "How should I take BONIVA?").**
- **Stop taking BONIVA and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.**

2. **Low calcium levels in your blood (hypocalcemia).**
   BONIVA may lower the calcium levels in your blood. If you have low blood calcium before you start taking BONIVA, it may get worse during treatment. Your low blood calcium must be treated before you take BONIVA. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take BONIVA. Take calcium and vitamin D as your doctor tells you to.

3. **Bone, joint, or muscle pain.**
   Some people who take BONIVA develop severe bone, joint, or muscle pain.

4. **Severe jaw bone problems (osteonecrosis).**
   Severe jaw bone problems may happen when you take BONIVA. Your doctor may examine your mouth before you start BONIVA. Your doctor may tell you to see your dentist before you start BONIVA. It is important for you to practice good mouth care during treatment with BONIVA.

5. **Unusual thigh bone fractures.**
   Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.
What is BONIVA?
BONIVA is a prescription medicine used to treat or prevent osteoporosis in women after menopause. BONIVA helps increase bone mass and helps reduce the chance of having a spinal fracture (break).
It is not known how long BONIVA works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if BONIVA is still right for you.
It is not known if BONIVA is safe and effective in children.

Who should not take BONIVA?
Do not take BONIVA if you:
- Have certain problems with your esophagus, the tube that connects your mouth with your stomach
- Cannot stand or sit upright for at least 60 minutes
- Have low levels of calcium in your blood
- Are allergic to BONIVA or any of its ingredients. A list of ingredients is at the end of this leaflet

What should I tell my doctor before taking BONIVA?
Before you start BONIVA, be sure to talk to your doctor if you:
- Have problems with swallowing
- Have stomach or digestive problems
- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant, or plan to become pregnant. It is not known if BONIVA can harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if BONIVA passes into your milk and may harm your baby.

Tell your doctor and dentist about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how BONIVA works.
Especially tell your doctor if you take:
- antacids
- aspirin
- Nonsteroidal Anti-Inflammatory (NSAID) medicines

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.
How should I take BONIVA?
- Take BONIVA exactly as your doctor tells you.
- **BONIVA works only if taken on an empty stomach.**
- Take 1 BONIVA tablet, **after** you get up for the day and **before** taking your first food, drink, or other medicine.
- Take BONIVA while you are sitting or standing.
- **Do not chew or suck on a tablet of BONIVA.**
- Swallow BONIVA tablet with a full glass (6-8 oz) of plain water only.
- Do **not** take BONIVA with mineral water, coffee, tea, soda, or juice.

After swallowing BONIVA tablet, wait at least 60 minutes:
- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take your first food or drink except for plain water.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 60 minutes after you take BONIVA and do not eat your first food of the day for at least 60 minutes after you take BONIVA.
If you miss a dose of BONIVA, do not take it later in the day. Call your doctor for instructions.
If you take too much BONIVA, call your doctor. Do not try to vomit. Do not lie down.

What are the possible side effects of BONIVA?
BONIVA may cause serious side effects.
• See **"What is the most important information I should know about BONIVA?"**

The most common side effects of BONIVA are:
• Back pain

• Heartburn

• Stomach area (abdominal) pain

• Pain in your arms and legs

• Diarrhea

• Headache

• Muscle pain

• Flu-like symptoms

You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue or throat.
Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of BONIVA. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How do I store BONIVA?
• Store BONIVA at room temperature, 59°F to 86°F (15°C to 30°C).

• Keep BONIVA in a tightly closed container.

Keep BONIVA and all medicines out of the reach of children.
General information about the safe and effective use of BONIVA.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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.
This Medication Guide summarizes the most important information about BONIVA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about BONIVA that is written for health professionals.
For more information, go to www.myboniva.com or call 1-888-692-6648.
What are the ingredients in BONIVA?
Active ingredient: ibandronate sodium
Inactive ingredients: lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. Tablet film coating contains: hypromellose, titanium dioxide, talc, polyethylene glycol 6000 and purified water.
This Medication Guide has been approved by the U.S. Food and Drug Administration.
Issued: January 2011
BONIVA is a registered trademark of Roche Therapeutics Inc.
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South San Francisco, CA 94080-4990
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Representative sample of labeling (see the HOW SUPPLIED section for complete listing):
PRINCIPAL DISPLAY PANEL - 150 mg Tablets Carton
NDC 0004-0186-82
once-monthly
Boniva®
(ibandronate sodium) Tablets
One tablet contains 168.75 mg ibandronate monosodium monohydrate,

equivalent to 150 mg free acid.
PHARMACIST: Dispense the enclosed Medication Guide to each patient.
USUAL DOSAGE: See package insert.
150 mg
3 Packs–One Tablet Per Pack
Rx only

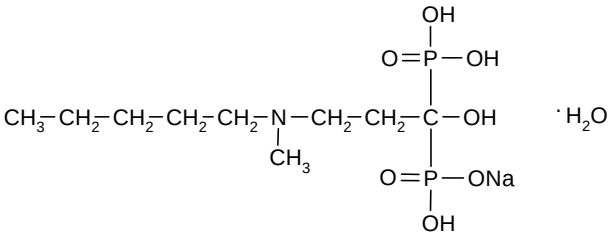
Revised: 01/2011 Distributed by: Genentech, Inc.

BONIVA®
(ibandronate sodium)
INJECTION

R_X only

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 Injection is intended for intravenous administration only. BONIVA Injection is available as a sterile, clear, colorless, ready-to-use solution in a prefilled syringe that delivers 3.375 mg of ibandronate monosodium salt monohydrate in 3 mL of solution, equivalent to a dose of 3 mg ibandronate free acid. Inactive ingredients include sodium chloride, glacial acetic acid, sodium acetate and 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

Distribution

Area under the serum ibandronate concentrations versus time curve increases in a dose-proportional manner after administration of 2 mg to 6 mg by intravenous injection.

After administration, 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 into the bone is estimated to be 40% to 50% of the circulating dose. In vitro protein binding in human serum was approximately 86% over

an ibandronate concentration range of 20 to 2000 ng/mL (approximate range of maximum serum ibandronate concentrations upon intravenous bolus administration) in one study.

Metabolism

There is no evidence that ibandronate is metabolized in humans. Ibandronate does not inhibit human P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 isozymes in vitro.

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 administered intravenous dose).

The plasma elimination of ibandronate is multiphasic. Its renal clearance and distribution into bone accounts for a rapid and early decline in plasma concentrations, reaching 10% of C_{max} within 3 or 8 hours after intravenous or oral administration, respectively. This is followed by a slower clearance phase as ibandronate redistributes back into the blood from bone. The observed apparent terminal half-life for ibandronate is generally dependent on the dose studied and on assay sensitivity. The observed apparent terminal half-life for intravenous 2 and 4 mg ibandronate after 2 hours of infusion ranges from 4.6 to 15.3 hours and 5 to 25.5 hours, respectively.

Following intravenous administration, 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 women) 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 pharmacokinetics of ibandronate is 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.

Melphalan/Prednisolone

A pharmacokinetic interaction study in multiple myeloma patients demonstrated that intravenous melphalan (10 mg/m^2) and oral prednisolone (60 mg/m^2) did not interact with 6 mg ibandronate upon intravenous coadministration. Ibandronate did not interact with melphalan or prednisolone.

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.

In studies of postmenopausal women, BONIVA Injection at doses of 0.5 mg to 3 mg produced biochemical changes indicative of inhibition of bone resorption, including decreases of biochemical markers of bone collagen degradation (cross-linked

C-telopeptide of Type I collagen [CTX]). Changes in markers of bone formation (osteocalcin) were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and formation.

Year 1 results from an efficacy and safety study comparing BONIVA Injection 3 mg every 3 months and BONIVA 2.5 mg daily oral tablet demonstrated that both dosing regimens significantly suppressed serum CTX levels at Months 3, 6, and 12. The median pre-dose or trough serum CTX levels in the ITT population reached a nadir of 57% (BONIVA Injection) and 62% (BONIVA 2.5 mg tablets) below baseline values by Month 6, and remained stable at Month 12 of treatment.

Clinical Studies

Daily Oral Tablets

The effectiveness and safety of BONIVA daily oral tablets 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 postmenopause, who had lumbar spine bone mineral density (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 two 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.

Quarterly IV Injection

The effectiveness and safety of BONIVA Injection 3 mg once every 3 months were demonstrated in a randomized, double-blind, multinational, noninferiority study (DIVA Study) in 1358 women with postmenopausal osteoporosis (L2-L4 lumbar spine BMD, T-score below -2.5 SD at baseline). The control group received BONIVA 2.5 mg daily oral tablets. The primary efficacy parameter was the relative change from baseline to 1 year of treatment in lumbar spine BMD, which was compared between the intravenous injection and the daily oral treatment groups. All patients received 400 IU vitamin D and 500 mg calcium supplementation per day.

Effect on Vertebral Fracture

BONIVA 2.5 mg daily oral tablet significantly reduced the incidence of new vertebral and of new and worsening vertebral fractures (Daily Oral Tablet – Treatment Study). 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 daily oral tablet ($p<0.001$) (see **Table 1**). In an unapproved regimen, intermittent oral administration of 20 mg BONIVA, involving a 9- to 10-week drug-free interval,

produced a statistically significant reduction (50%) in the incidence of new vertebral fractures, similar to that seen with the daily oral 2.5 mg regimen.

Table 1 Effect of BONIVA Daily Oral Tablet on the Incidence of Vertebral Fracture in the 3-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 postbaseline 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 at 3 years reported in women treated with BONIVA 2.5 mg daily oral tablet [9.1%, (95% CI: 7.1%, 11.1%)] and placebo [8.2%, (95% 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 (Daily Oral Tablet - Treatment Study).

Effect on Bone Mineral Density (BMD)

Daily Oral Tablet - Treatment Study: BONIVA 2.5 mg daily oral tablet 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 daily oral tablet 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 time points. Lumbar spine BMD increased by 6.4% after 3 years of treatment with BONIVA 2.5 mg daily oral tablet 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.

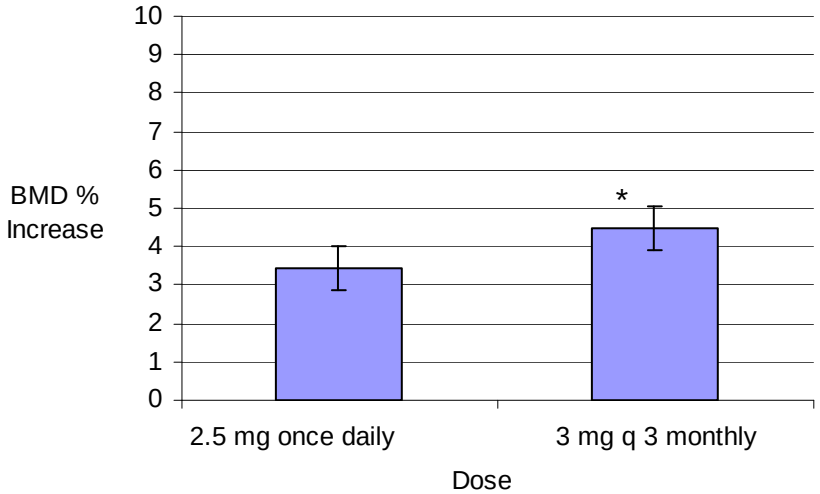
Table 2 Mean Percent Change in BMD from Baseline to Endpoint in Patients Treated with BONIVA 2.5 mg Daily Oral Tablet or Placebo in the 3-Year Osteoporosis Treatment Study*

	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 postbaseline value prior to the study's last time point is used.

Quarterly IV Injection – DIVA Study: In the ITT efficacy analysis, the least-squares mean increase at 1 year in lumbar spine BMD in patients (n=429) treated with BONIVA Injection 3 mg once every 3 months (4.5%) was statistically superior to that in patients (n=434) treated with daily oral tablets (3.5%). The mean difference between groups was 1.05% (95% CI: 0.53%, 1.57%; p<0.001; see **Figure 1**). The mean increases from baseline in total hip BMD at 1 year were 2.1% in the BONIVA Injection 3 mg once every 3 months group and 1.5% in the BONIVA 2.5 mg daily oral tablet group. Consistently higher BMD increases at the femoral neck and trochanter were also observed following BONIVA Injection 3 mg once every 3 months compared to BONIVA 2.5 mg daily oral tablet.

Figure 1 Mean Percent Change (95% CI) from Baseline in Lumbar Spine BMD at One Year in Patients Treated with BONIVA 2.5 mg Daily Oral Tablet or BONIVA Injection 3 mg Once Every 3 Months



* 3 mg q 3 mo vs 2.5 mg daily: p<0.001

Bone Histology

The effects of BONIVA 2.5 mg daily oral tablet 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.

The histological analysis of bone biopsies after 22 months of treatment with 3 mg intravenous ibandronate every 3 months (n=30) or 23 months of treatment with 2 mg intravenous ibandronate every 2 months (n=27) in women with postmenopausal osteoporosis showed bone of normal quality and no indication of a mineralization defect.

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 Injection administered at a therapeutic dose 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 8 to 4 times the human intravenous dose of 3 mg every 3 months, based on cumulative dose normalized for body surface area (mg/m^2) and AUC comparison, respectively. 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 Injection is indicated for the treatment of osteoporosis in postmenopausal women.

In postmenopausal women with osteoporosis, BONIVA increases BMD and reduces the incidence of vertebral fractures (see **CLINICAL PHARMACOLOGY: 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 2.0 standard deviations below the premenopausal mean [ie, T-score]).

The safety and effectiveness of BONIVA for the treatment of osteoporosis are based on clinical data of one year duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

CONTRAINDICATIONS

- Known hypersensitivity to BONIVA Injection or to any of its excipients
- Uncorrected hypocalcemia (see **PRECAUTIONS: General**)

WARNINGS

BONIVA Injection, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values (see **PRECAUTIONS**).

BONIVA Injection must only be administered intravenously. Care must be taken not to administer BONIVA Injection intra-arterially or paravenously as this could lead to tissue damage.

Do not administer BONIVA Injection by any other route of administration. The safety and efficacy of BONIVA Injection following non-intravenous routes of administration have not been established.

PRECAUTIONS

General

Mineral Metabolism

Hypocalcemia, hypovitaminosis D, and other disturbances of bone and mineral metabolism must be effectively treated before starting BONIVA Injection therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients must receive supplemental calcium and vitamin D.

Renal Impairment

Treatment with intravenous bisphosphonates has been associated with renal toxicity manifested as deterioration in renal function (ie, increased serum creatinine) and in rare cases, acute renal failure. No cases of acute renal failure were observed in controlled clinical trials in which intravenous BONIVA was administered as a 15- to 30-second bolus. The risk of serious renal toxicity with other intravenous bisphosphonates appears to be inversely related to the rate of drug administration.

Patients who receive BONIVA Injection should have serum creatinine measured prior to each dosage administration. Patients with concomitant diseases that have the potential for adverse effects on the kidney or patients who are taking concomitant medications that have the potential for adverse effects on the kidney should be assessed, as clinically appropriate. Treatment should be withheld for renal deterioration.

BONIVA Injection should not be administered to patients with severe renal impairment (ie, patients with serum creatinine >200 μmol/L [2.3 mg/dL] or creatinine clearance [measured or estimated] <30 mL/min).

Jaw Osteonecrosis

Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures,

but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.

For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). However, such reports have been infrequent. This category of drugs includes BONIVA (ibandronate sodium) Injection. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low-trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Information for Patients

BONIVA Injection must be administered intravenously only by a health care professional. Patients should be instructed to read the Medication Guide carefully before taking BONIVA, and to re-read it each time the prescription is renewed because it contains important information the patient should know about BONIVA.

BONIVA Injection should be administered once every 3 months. If the dose is missed, the injection should be administered as soon as it can be rescheduled. Thereafter, injections should be scheduled every 3 months from the date of the last injection. Do not administer BONIVA Injection more frequently than once every 3 months.

Patients must receive supplemental calcium and vitamin D.

Drug Interactions

See **CLINICAL PHARMACOLOGY: Drug Interactions**

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 3 and 1 times, respectively, human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative 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 96 and 14 times, respectively, human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative 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 (32 to 51 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative 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, and increased preimplantation loss were observed at an intravenous dose of 1.2 mg/kg/day (117 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In male rats treated for 28 days prior to mating, a decrease in sperm production and altered sperm morphology were observed at intravenous doses ≥0.3 mg/kg/day (≥40 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison).

Pregnancy

Pregnancy Category C

In pregnant rats given intravenous doses of 0.05, 0.15, or 0.5 mg/kg/day from Day 17 post-coitum until Day 20 post-partum, ibandronate treatment resulted in dystocia, maternal mortality, and early postnatal pup loss in all dose groups (≥2 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). Reduced body weight at birth was observed at 0.15 and 0.5 mg/kg/day (≥4 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). Pups exhibited abnormal odontogeny that decreased food consumption and body weight gain at 0.15 and 0.5 mg/kg/day (≥18 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative 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 an intravenous dose of 1 mg/kg/day (≥47 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In this spontaneous delivery study, dystocia was counteracted by perinatal calcium supplementation. In rat studies with intravenous dosing during gestation, fetal weight and pup growth were reduced at doses ≥0.1 mg/kg/day (≥5 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison).

In pregnant rabbits given intravenous doses of 0.03, 0.07 or 0.2 mg/kg/day during the period of organogenesis, maternal mortality, reduced maternal body weight gain, decreased litter size due to increased resorption rate, and decreased fetal weight were observed at 0.2 mg/kg/day (19 times the recommended human intravenous dose of 3 mg every 3 months, based on cumulative body surface area comparison, mg/m^2).

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into

maternal bone. Therefore, there is a theoretical risk of fetal harm (eg, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

There are no adequate and well-controlled studies in pregnant women. BONIVA Injection 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 Injection 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 Injection 3 mg every 3 months for 1 year (DIVA study), 51% were over 65 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

Daily Oral Tablet

Treatment with BONIVA 2.5 mg daily oral tablet was 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 tablet in these studies was similar to that of placebo.

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 oral tablet group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily oral tablet group and the placebo group. Overall, and according to body system, there was no difference between BONIVA daily oral tablet 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 2.5 mg daily oral tablet 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 2.5 mg Daily Oral Tablet than in Patients Treated with Placebo in the Osteoporosis Treatment and Prevention Studies

Body System	Placebo % (n=1134)	BONIVA 2.5 mg daily % (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

Quarterly IV Injection – DIVA Study

In a 1-year, double-blind, multicenter study comparing BONIVA Injection administered intravenously as 3 mg every 3 months to BONIVA 2.5 mg daily oral tablet in women with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two

dosing regimens were similar. The incidence of serious adverse events was 8.0% in the BONIVA 2.5 mg daily group and 7.5% in the BONIVA Injection 3 mg once every 3 months group. The percentage of patients who withdrew from treatment due to adverse events was approximately 6.7% in the BONIVA 2.5 mg daily group and 8.5% in the BONIVA Injection 3 mg every 3 months group.

Table 4 lists the adverse events reported in >2% of patients without attribution of causality.

Table 4 Adverse Events With an Incidence of at Least 2% in Patients Treated with BONIVA Injection (3 mg once every 3 months) or BONIVA Daily Oral Tablet (2.5 mg)

Body System/Adverse Event	BONIVA 2.5 mg Daily (Oral) % (n=465)	BONIVA 3 mg q 3 mo (IV) % (n=469)
Infections and Infestations		
Influenza	8.0	4.7
Nasopharyngitis	6.0	3.4
Cystitis	3.4	1.9
Gastroenteritis	3.4	1.5
Urinary Tract Infection	3.2	2.6
Bronchitis	2.8	2.1
Upper Respiratory Tract Infection	2.8	1.1
Gastrointestinal Disorders		
Abdominal Pain*	5.6	5.1
Dyspepsia	4.3	3.6
Nausea	4.3	2.1
Constipation	4.1	3.4
Diarrhea	2.4	2.8
Gastritis	2.2	1.9
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	8.6	9.6
Back Pain	7.5	7.0
Localized Osteoarthritis	2.4	1.5
Pain in Extremity	2.2	2.8
Myalgia	0.9	2.8
Nervous System Disorders		
Dizziness	2.8	1.9
Headache	2.6	3.6
Vascular Disorders		
Hypertension	7.1	5.3
Psychiatric Disorders		
Insomnia	2.6	1.1
Depression	2.2	1.3

General Disorders and Administration Site Conditions		
Influenza-like Illness†	1.1	4.9
Fatigue	1.1	2.8
Skin and Subcutaneous Tissue Disorders		
Rash‡	2.8	2.3
Metabolism and Nutrition Disorders		
Hypercholesterolemia	4.3	1.5

* Is a combination of abdominal pain and abdominal pain upper
† Combination of influenza-like illness and acute phase reaction
‡ Combination of rash, rash pruritic, rash macular, dermatitis, dermatitis allergic, exanthem, erythema, rash papular, rash generalized, dermatitis medicamentosa, rash erythematous

Acute Phase Reaction-like Events

Symptoms consistent with acute phase reaction (APR) have been reported with intravenous bisphosphonate use. The overall incidence of patients with APR-like events was higher in the intravenous treatment group (4% in the BONIVA 2.5 mg daily oral tablet group vs. 10% in the BONIVA Injection 3 mg once every 3 months group). These incidence rates are based on reporting of any of 33 potential APR-like symptoms within 3 days of an IV dose and for a duration of 7 days or less. In most cases, no specific treatment was required and the symptoms subsided within 24 to 48 hours.

Injection Site Reactions

Local reactions at the injection site, such as redness or swelling, were observed infrequently, but at a higher incidence in patients treated with BONIVA Injection 3 mg every 3 months (<2%; 8/469) than in patients treated with placebo injections (<1%; 1/465). In most cases, the reaction was of mild to moderate severity.

Ocular Adverse Events

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 with oral ibandronate. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen with 2.5 mg daily oral ibandronate compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. There also was no evidence that BONIVA Injection 3 mg every 3 months induced clinically significant laboratory abnormalities indicative of hepatic or renal dysfunction compared to BONIVA 2.5 mg daily oral tablet.

OVERDOSAGE

No cases of overdose were reported in premarketing studies with BONIVA Injection. Intravenous overdosage may result in hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

Dialysis would not be beneficial unless it is administered within 2 hours following the overdose.

DOSAGE AND ADMINISTRATION

The recommended dose of BONIVA Injection for the treatment of postmenopausal osteoporosis is 3 mg every 3 months (see **INDICATIONS AND USAGE**) administered over a period of 15 to 30 seconds.

No cases of acute renal failure were observed in controlled clinical trials in which intravenous BONIVA was administered as a 15- to 30-second bolus. The risk of serious renal toxicity with other intravenous bisphosphonates appears to be inversely related to the rate of drug administration (see **PRECAUTIONS**).

BONIVA Injection must be administered by a health care professional.

BONIVA Injection must only be administered intravenously (see **WARNINGS**). Care must be taken not to administer BONIVA Injection intra-arterially or paravenously as this could lead to tissue damage.

Do not administer BONIVA Injection by any other route of administration. The safety and efficacy of BONIVA Injection following non-intravenous routes of administration have not been established.

Administer BONIVA Injection using the enclosed needle. Prefilled syringes are for single use only. Discard unused portion.

BONIVA Injection must not be mixed with calcium-containing solutions or other intravenously administered drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, and not used if particulate matter is visible or product is discolored. Prefilled syringes with particulate matter or discoloration should not be used.

If the dose is missed, BONIVA Injection should be administered as soon as it can be rescheduled. Thereafter, injections should be scheduled every 3 months from the date of the last injection. Do not administer BONIVA Injection (3 mg) more frequently than once every 3 months.

Patients must receive supplemental calcium and vitamin D (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 Injection should not be administered to patients with severe renal impairment, ie, patients with serum creatinine >200 μmol/L (2.3 mg/dL) or creatinine clearance (measured or estimated) <30 mL/min (see **CLINICAL PHARMACOLOGY: Special Populations**).

Geriatric Patients

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

HOW SUPPLIED

One prefilled syringe of BONIVA Injection (ibandronate sodium), 3 mg/3 mL single-use, clear glass prefilled syringe, in a box with 1 needle and 2 alcohol swabs (NDC 0004-0188-09).

Each syringe is a 5 mL (5 cc) volume syringe supplied with a 25-gauge, 3/4 inch needle with wings, needle-stick protection device, and a 9 cm plastic tubing for attachment.

Storage

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

BONIVA is a registered trademark of Roche Therapeutics Inc.

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MEDICATION GUIDE

Boniva® (bon-EE-va)
(ibandronate sodium)
Injection

Read the Medication Guide that comes with BONIVA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about BONIVA.

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

BONIVA Injection is given in your vein (intravenously) and only given by a healthcare provider. Do not give BONIVA Injection to yourself.

BONIVA can cause serious side effects including:

1. Low calcium levels in your blood (hypocalcemia)
2. Severe kidney problems
3. Severe jaw bone problems (osteonecrosis)
4. Bone, joint or muscle pain
5. Unusual thigh bone fractures

1. **Low calcium levels in your blood (hypocalcemia).**

   BONIVA may lower the calcium levels in your blood. If you have low blood calcium before you start taking BONIVA, it may get worse during treatment. Your low blood calcium must be treated before you take BONIVA. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

   - Spasms, twitches, or cramps in your muscles
   - Numbness or tingling in your fingers, toes, or around your mouth

   Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take BONIVA. Take calcium and vitamin D as your doctor tells you to.

2. **Severe kidney problems.**

   Severe kidney problems, including kidney failure, may happen when you take BONIVA. Your doctor should perform blood tests to check your kidneys before you receive each treatment.

3. **Severe jaw bone problems (osteonecrosis).**

   Severe jaw bone problems may happen when you take BONIVA. Your doctor may examine your mouth before you start BONIVA. Your doctor may tell you to see your dentist before you start BONIVA. It is important for you to practice good mouth care during treatment with BONIVA.

4. **Bone, joint, or muscle pain.**

   Some people who take BONIVA develop severe bone, joint, or muscle pain.

5. **Unusual thigh bone fractures.**

   Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is BONIVA?

BONIVA is a prescription medicine used to treat osteoporosis in women after menopause. BONIVA helps increase bone mass and helps reduce the chance of having a spinal fracture (break).

It is not known how long BONIVA works for the treatment of osteoporosis. You should see your doctor regularly to determine if BONIVA is still right for you.

It is not known if BONIVA is safe and effective in children.

Who should not take BONIVA?

Do not take BONIVA if you:

- Have low levels of calcium in your blood
- Are allergic to BONIVA or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking BONIVA?

Before you start BONIVA, be sure to talk to your doctor if you:

- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems or other problems that may affect your kidneys
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Are pregnant, or plan to become pregnant. It is not known if BONIVA can harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if BONIVA passes into your milk and may harm your baby.

Tell your doctor and dentist about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Certain medicines may affect how BONIVA works.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How will I receive BONIVA?

- BONIVA Injection is given 1 time every 3 months by a healthcare provider.
- If you miss a dose of BONIVA, call your doctor or healthcare provider to schedule your next dose.

What are the possible side effects of BONIVA?

BONIVA may cause serious side effects.

- See **"What is the most important information I should know about BONIVA?"**

The most common side effects of BONIVA are:

- Pain in your bones, joints or muscles
- Flu-like symptoms (fever, chills, bone, joint, or muscle pain, fatigue)
- Headache

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BONIVA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I handle BONIVA if I need to pick it up from a pharmacy?

- Store BONIVA Injection at room temperature between 59° and 86°F (15° and 30°C).
- Keep BONIVA Injection and all medicines out of the reach of children.

General information about the safe and effective use of BONIVA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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.

This Medication Guide summarizes the most important information about BONIVA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about BONIVA that is written for health professionals.

For more information, go to www.myboniva.com or call 1-888-692-6648.

What are the ingredients in BONIVA?

Active ingredient: ibandronate sodium

Inactive ingredients: sodium chloride, glacial acetic acid, sodium acetate and water

Distributed by:

Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Reclast SAFELY AND EFFECTIVELY. See full prescribing information for RECLAST.

Reclast ® (zoledronic acid) Injection
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.6)	01/2011
Dosage and Administration (2, 2.6)	03/2011
Contraindications (4.2)	08/2011
Warnings and Precautions (5.3)	08/2011
Warnings and Precautions (5.5)	01/2011

----------INDICATIONS AND USAGE----------

Reclast is a bisphosphonate indicated for:

- Treatment and prevention of postmenopausal osteoporosis (1.1, 1.2)
- Treatment to increase bone mass in men with osteoporosis (1.3)
- Treatment and prevention of glucocorticoid-induced osteoporosis (1.4)
- Treatment of Paget's disease of bone in men and women (1.5)

The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis (1.6)

----------DOSAGE AND ADMINISTRATION----------

Infusion given intravenously over no less than 15 minutes:

- Treatment of postmenopausal osteoporosis (2.1); treatment to increase bone mass in men with osteoporosis (2.3): treatment and prevention of glucocorticoid-induced osteoporosis (2.4): 5 mg once a year
- Prevention of postmenopausal osteoporosis: 5 mg once every 2 years (2.2)
- Treatment of Paget's disease of bone: a single 5 mg infusion. Patients should receive 1500 mg elemental calcium and 800 IU vitamin D daily (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

5 mg in a 100 mL ready-to-infuse solution (3)

----------CONTRAINDICATIONS----------

- Hypocalcemia (4.1)
- Patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment (4.2, 5.3)
- Hypersensitivity to any component of Reclast (4.3, 6.2)

----------WARNINGS AND PRECAUTIONS----------

- Patients receiving Zometa should not receive Reclast (5.1)
- Patients must be adequately supplemented with calcium and vitamin D (5.2)
- A single dose should not exceed 5 mg and the duration of infusion should be no less than 15 minutes. Renal toxicity may be greater in patients with underlying renal impairment or with other risk factors, including advanced age or dehydration. Monitor creatinine clearance before each dose (2.1, 2.2, 5.3)
- Osteonecrosis of the jaw has been reported. All patients should have a routine oral exam by the prescriber prior to treatment (5.4)
- Atypical femur fractures have been reported. Patients with thigh or groin pain should be evaluated to rule out a femoral fracture (5.5).
- Reclast can cause fetal harm. Women of childbearing potential should be advised (5.6, 8.1)
- Severe incapacitating bone, joint, and/or muscle pain may occur. Withhold future doses of Reclast if severe symptoms occur (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions (>10%) were pyrexia, myalgia, headache, arthralgia, pain in extremity (6.1). Other important adverse reactions were flu-like illness, nausea, vomiting, diarrhea (6.2), and eye inflammation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Aminoglycosides: May lower serum calcium for prolonged periods (7.1)
- Loop diuretics: May increase risk of hypocalcemia (7.2)
- Nephrotoxic drugs: Use with caution (7.3)
- Drugs primarily excreted by the kidney: Exposure may be increased with renal impairment. Monitor serum creatinine in patients at risk (7.4)

----------USE IN SPECIFIC POPULATIONS-----

Nursing Mothers: Reclast should not be given to nursing women (8.3)
Pediatric Use: Not indicated for use in pediatric patients (8.4)
Geriatric Use: Special care to monitor renal function (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2011

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Reference ID: 3008875

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Osteoporosis in Postmenopausal Women

Reclast is indicated for treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, diagnosed by bone mineral density (BMD) or prevalent vertebral fracture, Reclast reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures). In patients at high risk of fracture, defined as a recent low-trauma hip fracture, Reclast reduces the incidence of new clinical fractures [*see Clinical Studies (14.1)*].

1.2 Prevention of Osteoporosis in Postmenopausal Women

Reclast is indicated for prevention of osteoporosis in postmenopausal women [*see Clinical Studies (14.2)*].

1.3 Osteoporosis in Men

Reclast is indicated for treatment to increase bone mass in men with osteoporosis [*see Clinical Studies (14.3)*].

1.4 Glucocorticoid-Induced Osteoporosis

Reclast is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who are expected to remain on glucocorticoids for at least 12 months [*see Clinical Studies (14.4)*].

1.5 Paget's Disease of Bone

Reclast is indicated for treatment of Paget's disease of bone in men and women. Treatment is indicated in patients with Paget’s disease of bone with elevations in serum alkaline phosphatase of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease [*see Clinical Studies (14.5)*].

1.6 Important Limitations of Use

The safety and effectiveness of Reclast for the treatment of osteoporosis is based on clinical data of three years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

2 DOSAGE AND ADMINISTRATION

A 5 mg dose of Reclast administered intravenously is recommended for patients with creatinine clearance ≥ 35 mL/min [*see Warnings and Precautions (5.3)*]

Reclast is contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment [see Contraindications (4.2)].

There are no safety or efficacy data to support the adjustment of the Reclast dose based on baseline renal function. Therefore, no dose adjustment is required in patients with CrCl ≥ 35 mL/min.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Patients must be appropriately hydrated prior to administration of Reclast [*see Warnings and Precautions (5.3)*].

The i.v. infusion should be followed by a 10 mL normal saline flush of the intravenous line.

Administration of acetaminophen following Reclast administration may reduce the incidence of acute-phase reaction symptoms.

2.1 Treatment of Osteoporosis in Postmenopausal Women

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes. For osteoporosis treatment, and to reduce the risk of hypocalcemia, patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. Postmenopausal women require an average of at least 1200 mg calcium and 800-1000 IU vitamin D daily.

Reference ID: 3008875

2.2 Prevention of Osteoporosis in Postmenopausal Women

The recommended regimen is a 5 mg infusion given once every 2 years intravenously over no less than 15 minutes. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. Postmenopausal women require an average of 1200 mg calcium and 800-1000 IU vitamin D daily.

2.3 Osteoporosis in Men

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. An average of at least 1200 mg calcium and 800-1000 IU vitamin D daily is recommended.

2.4 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. An average of at least 1200 mg calcium and 800-1000 IU vitamin D daily is recommended.

2.5 Treatment of Paget's Disease of Bone

The recommended dose is a 5 mg infusion. The infusion time must not be less than 15 minutes given over a constant infusion rate.

To reduce the risk of hypocalcemia, all patients with Paget's disease should receive 1500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D daily, particularly in the 2 weeks following Reclast administration. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcemia [*see Warnings and Precautions (5.2)*].

Re-treatment of Paget's Disease

After a single treatment with Reclast in Paget's disease an extended remission period is observed. Specific re-treatment data are not available. However, re-treatment with Reclast may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, or in those patients who failed to achieve normalization of their serum alkaline phosphatase, or in those patients with symptoms, as dictated by medical practice.

2.6 Method of Administration

The Reclast infusion time must not be less than 15 minutes given over a constant infusion rate.

The i.v. infusion should be followed by a 10 mL normal saline flush of the intravenous line.

Reclast solution for infusion must not be allowed to come in contact with any calcium or other divalent cation-containing solutions, and should be administered as a single intravenous solution through a separate vented infusion line.

If refrigerated, allow the refrigerated solution to reach room temperature before administration. After opening, the solution is stable for 24 hours at 2°C–8°C (36°F - 46°F) [*see How Supplied/Storage and Handling (16)*].

3 DOSAGE FORMS AND STRENGTHS

5 mg in a 100 mL ready to infuse solution.

4 CONTRAINDICATIONS

4.1 Hypocalcemia

[*See Warnings and Precautions (5.2).*]

4.2 Renal Failure

Reclast is contraindicated in patients with creatinine clearance < 35 ml/min and in those with evidence of acute renal impairment due to an increased risk of renal failure [see Warnings and Precautions (5.3)]

4.3 Hypersensitivity to Zoledronic Acid or Any Components of Reclast

Hypersensitivity reactions including rare cases of urticaria, angioedema, and anaphylactic reaction/shock have been reported [*see Post-Marketing Experience (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with Same Active Ingredient

Reclast contains the same active ingredient found in Zometa, used for oncology indications, and a patient being treated with Zometa should not be treated with Reclast.

5.2 Hypocalcemia and Mineral Metabolism

Pre-existing hypocalcemia and disturbances of mineral metabolism (e.g., hypoparathyroidism, thyroid surgery, parathyroid surgery; malabsorption syndromes, excision of small intestine) must be effectively treated before initiating therapy with Reclast. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended for these patients [*see Contraindications (4)*].

Hypocalcemia following Reclast administration is a significant risk in Paget's disease. All patients should be instructed about the symptoms of hypocalcemia and the importance of calcium and vitamin D supplementation in maintaining serum calcium levels [*see Dosage and Administration (2), Adverse Reactions (6.1), Information for Patients (17)*].

All osteoporosis patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels [*see Dosage and Administration (2), Adverse Reactions (6.1), Information for Patients (17)*].

5.3 Renal Impairment

A single dose of Reclast should not exceed 5 mg and the duration of infusion should be no less than 15 minutes [*see Dosage and Administration (2.1)*]**.**

Reclast is contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment. [*See Contraindications (4.2)*]. If history or physical signs suggest dehydration, Reclast therapy should be withheld until normovolemic status has been achieved. [*See Post-marketing Experience (6.2)*]

Reclast should be used with caution in patients with chronic renal impairment. Acute renal impairment, including renal failure, has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise, advanced age, concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after Reclast administration. Acute renal failure (ARF) has been observed in patients after a single administration. Rare reports of hospitalization and/or dialysis or fatal outcome occurred in patients with underlying moderate to severe renal impairment or with any of the risk factors described in this section [*see Post-Marketing Experience (6.2)*]. Renal impairment may lead to increased exposure of concomitant medications and/or their metabolites that are primarily renally excreted [*see Drug Interactions (7.4)*].

Creatinine clearance should be calculated based on actual body weight using Cockcroft-Gault formula before each Reclast dose. Transient increase in serum creatinine may be greater in patients with impaired renal function; interim monitoring of creatinine clearance should be performed in at-risk patients. Elderly patients and those receiving diuretic therapy are at increased risk of acute renal failure. These patients should have their fluid status assessed and be appropriately hydrated prior to administration of Reclast. Reclast should be used with caution with other nephrotoxic drugs [*see Drug Interactions (7.3)*]. Consider monitoring creatinine clearance in patients at-risk for ARF who are taking concomitant medications that are primarily excreted by the kidney [*see Drug Interactions (7.4)*].

5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, including zoledronic acid. Most cases have been in cancer patients treated with intravenous bisphosphonates undergoing dental procedures. Some cases have occurred in patients with postmenopausal osteoporosis treated with either oral or intravenous bisphosphonates. A routine oral examination should be performed by the prescriber prior to initiation of bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy).

While on treatment, patients with concomitant risk factors should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. The clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment [*see Adverse Reactions (6.1)*].

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.6 Pregnancy

RECLAST SHOULD NOT BE USED DURING PREGNANCY. Reclast may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while on Reclast therapy [*see Use in Specific Populations (8.1)*].

5.7 Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Reclast. The time to onset of symptoms varied from one day to several months after starting the drug. Consider withholding future Reclast treatment if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate [*see Adverse Reactions (6.2)*].

5.8 Patients with Asthma

While not observed in clinical trials with Reclast, there have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates. Use Reclast with caution in aspirin-sensitive patients.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of Osteoporosis in Postmenopausal Women

The safety of Reclast in the treatment of postmenopausal osteoporosis was assessed in Study 1, a large, randomized, double-blind, placebo-controlled, multinational study of 7736 postmenopausal women aged 65-89 years with osteoporosis, diagnosed by bone mineral density or the presence of a prevalent vertebral fracture. The duration of the trial was three years with 3862 patients exposed to Reclast and 3852 patients exposed to placebo administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes, for a total of three doses. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was similar between groups: 3.4% in the Reclast group and 2.9% in the placebo group. The incidence of serious adverse events was 29.2% in the Reclast group and 30.1% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 5.4% and 4.8% for the Reclast and placebo groups, respectively.

The safety of Reclast in the treatment of osteoporosis patients with a recent (within 90 days) low-trauma hip fracture was assessed in Study 2, a randomized, double-blind, placebo-controlled, multinational endpoint-driven study of 2127 men and women aged 50-95 years; 1065 patients were randomized to Reclast and 1062 patients were randomized to placebo. Reclast was administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. The study continued until at least 211 patients had a confirmed clinical fracture in the study population who were followed for an average of approximately 2 years on study drug. Vitamin D levels were not routinely measured but a loading dose of

vitamin D (50,000 to 125,000 IU orally or IM) was given to patients and they were started on 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day for at least 14 days prior to the study drug infusions.

The incidence of all-cause mortality was 9.6% in the Reclast group and 13.3% in the placebo group. The incidence of serious adverse events was 38.3% in the Reclast group and 41.3% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 5.3% and 4.7% for the Reclast and placebo groups, respectively.

Adverse reactions reported in at least 2% of patients with osteoporosis and more frequently in the Reclast-treated patients than placebo-treated patients in either osteoporosis trial are shown below in Table 1.

Table 1. Adverse Reactions Occurring in ≥ 2.0% of Patients with Osteoporosis and More Frequently than in Placebo-Treated Patients

	Study 1		Study 2	
System Organ Class	**5 mg IV Reclast once per year % (N=3862)**	**Placebo once per year % (N=3852)**	**5 mg IV Reclast once per year % (N=1054)**	**Placebo once per year % (N=1057)**
Blood and the Lymphatic System Disorders				
Anemia	4.4	3.6	5.3	5.2
Metabolism and Nutrition Disorders				
Dehydration	0.6	0.6	2.5	2.3
Anorexia	2.0	1.1	1.0	1.0
Nervous System Disorders				
Headache	12.4	8.1	3.9	2.5
Dizziness	7.6	6.7	2.0	4.0
Ear and Labyrinth Disorders				
Vertigo	4.3	4.0	1.3	1.7
Cardiac Disorders				
Atrial Fibrillation	2.4	1.9	2.8	2.6
Vascular Disorders				
Hypertension	12.7	12.4	6.8	5.4
Gastrointestinal Disorders				
Nausea	8.5	5.2	4.5	4.5
Diarrhea	6.0	5.6	5.2	4.7
Vomiting	4.6	3.2	3.4	3.4
Abdominal Pain Upper	4.6	3.1	0.9	1.5
Dyspepsia	4.3	4.0	1.7	1.6
Musculoskeletal, Connective Tissue and Bone Disorders				
Arthralgia	23.8	20.4	17.9	18.3
Myalgia	11.7	3.7	4.9	2.7
Pain in Extremity	11.3	9.9	5.9	4.8
Shoulder Pain	6.9	5.6	0.0	0.0
Bone Pain	5.8	2.3	3.2	1.0
Neck Pain	4.4	3.8	1.4	1.1
Muscle Spasms	3.7	3.4	1.5	1.7
Osteoarthritis	9.1	9.7	5.7	4.5
Musculoskeletal Pain	0.4	0.3	3.1	1.2
General Disorders and Administrative Site Conditions				
Pyrexia	17.9	4.6	8.7	3.1
Influenza-like Illness	8.8	2.7	0.8	0.4
Fatigue	5.4	3.5	2.1	1.2
Chills	5.4	1.0	1.5	0.5
Asthenia	5.3	2.9	3.2	3.0
Peripheral Edema	4.6	4.2	5.5	5.3
Pain	3.3	1.3	1.5	0.5
Malaise	2.0	1.0	1.1	0.5
Hyperthermia	0.3	<0.1	2.3	0.3
Chest Pain	1.3	1.1	2.4	1.8
Investigations				
Creatinine Renal Clearance Decreased	2.0	2.4	2.1	1.7

Renal Impairment

Treatment with intravenous bisphosphonates, including zoledronic acid, has been associated with renal impairment manifested as deterioration in renal function (i.e., increased serum creatinine) and in rare cases, acute renal failure. In the

clinical trial for postmenopausal osteoporosis, patients with baseline creatinine clearance < 30 mL/min (based on actual body weight), urine dipstick ≥2+ protein or increase in serum creatinine of >0.5 mg/dL during the screening visits were excluded. The change in creatinine clearance (measured annually prior to dosing) and the incidence of renal failure and impairment was comparable for both the Reclast and placebo treatment groups over 3 years, including patients with creatinine clearance between 30-60 mL/min at baseline. Overall, there was a transient increase in serum creatinine observed within 10 days of dosing in 1.8% of Reclast-treated patients versus 0.8% of placebo-treated patients which resolved without specific therapy [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

The signs and symptoms of acute phase reaction occurred in Study 1 following Reclast infusion including fever (18%), myalgia (9%), flu-like symptoms (8%), headache (7%), and arthralgia (7%). The majority of these symptoms occurred within the first 3 days following the dose of Reclast and usually resolved within 3 days of onset but resolution could take up to 7-14 days. In Study 2, patients without a contraindication to acetaminophen were provided with a standard oral dose at the time of the IV infusion and instructed to use additional acetaminophen at home for the next 72 hours as needed. Reclast was associated with fewer signs and symptoms of a transient acute phase reaction in this trial: fever (7%) and arthralgia (3%). The incidence of these symptoms decreased with subsequent doses of Reclast.

Laboratory Findings

In Study 1, in women with postmenopausal osteoporosis, approximately 0.2% of patients had notable declines of serum calcium levels (less than 7.5 mg/dL) following Reclast administration. No symptomatic cases of hypocalcemia were observed. In Study 2, following pre-treatment with vitamin D, no patients had treatment emergent serum calcium levels below 7.5 mg/dL.

Injection Site Reactions

In the osteoporosis trials, local reactions at the infusion site such as itching, redness and/or pain have been reported in 0% to 0.7% of patients following the administration of Reclast and 0% to 0.5% of patients following administration of placebo.

Osteonecrosis of the Jaw

In the postmenopausal osteoporosis trial, Study 1, in 7736 patients, after initiation of therapy, symptoms consistent with ONJ occurred in one patient treated with placebo and one patient treated with Reclast. Both cases resolved after appropriate treatment [*see Warnings and Precautions (5.4)*]. No reports of osteonecrosis of the jaw were reported in either treatment group in Study 2.

Atrial Fibrillation

In the postmenopausal osteoporosis trial, Study 1, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occurred in 1.3% of patients (50 out of 3862) compared to 0.4% (17 out of 3852) in the placebo group. The overall incidence of all atrial fibrillation adverse events in the zoledronic acid treatment group was reported in 2.5% of patients (96 out of 3862) in the Reclast group vs. 1.9% of patients (75 out of 3852) in the placebo group. Over 90% of these events in both treatment groups occurred more than a month after the infusion. In an ECG sub-study, ECG measurements were performed on a subset of 559 patients before and 9 to 11 days after treatment. There was no difference in the incidence of atrial fibrillation between treatment groups suggesting these events were not related to the acute infusions. In Study 2, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occurred in 1.0% of patients (11 out of 1054) compared to 1.2% (13 out of 1057) in the placebo group demonstrating no difference between treatment groups.

Ocular Adverse Events

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the osteoporosis trials, 1 (<0.1%) to 9 (0.2%) patients treated with Reclast and 0 (0%) to 1 (<0.1%) patient treated with placebo developed iritis/uveitis/episcleritis.

<u>Prevention of Osteoporosis in Postmenopausal Women</u>

The safety of Reclast in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged ≥45 years. Patients were randomized to one of three treatment groups: (1) Reclast given at randomization and Month 12 (n=198); (2) Reclast given at randomization and placebo at Month 12 (n=181); and (3) placebo given at randomization and Month 12 (n=202).

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Reclast was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day.

The incidence of serious adverse events was similar for subjects given (1) Reclast at randomization and at Month 12 (10.6%), (2) Reclast at randomization and placebo given at Month 12 (9.4%), and (3) placebo at randomization and at Month 12 (11.4%). The percentages of patients who withdrew from the study due to adverse events were 7.1%, 7.2%, and 3.0% in the two Reclast groups and placebo group, respectively. Adverse reactions reported in at least 2% of patients with osteopenia and more frequently in the Reclast-treated patients than placebo-treated patients are shown in Table 2.

Table 2. Adverse Reactions Occurring in ≥ 2% of Patients with Osteopenia and More Frequently than in Placebo-Treated Patients

System Organ Class	5 mg IV Reclast Once Per Year % (n=198)	5 mg IV Reclast Once % (n=181)	Placebo once per year % (n=202)
Metabolism and nutrition disorders			
Anorexia	2.0	0.6	0.0
Nervous system disorders			
Headache	14.6	20.4	11.4
Dizziness	7.6	6.1	3.5
Hypoesthesia	5.6	2.2	2.0
Ear and labyrinth disorders			
Vertigo	2.0	1.7	1.0
Vascular disorders			
Hypertension	5.1	8.3	6.9
Gastrointestinal disorders			
Nausea	17.7	11.6	7.9
Diarrhea	8.1	6.6	7.9
Vomiting	7.6	5.0	4.5
Dyspepsia	7.1	6.6	5.0
Abdominal pain*	8.6	6.6	7.9
Constipation	6.6	7.2	6.9
Abdominal discomfort	2.0	1.1	0.5
Abdominal distension	2.0	0.6	0.0
Skin and subcutaneous tissue disorders			
Rash	3.0	2.2	2.5
Musculoskeletal and connective tissue disorders			
Arthralgia	27.3	18.8	19.3
Myalgia	19.2	22.7	6.9
Back pain	18.2	16.6	11.9
Pain in extremity	11.1	16.0	9.9
Muscle spasms	5.6	2.8	5.0
Musculoskeletal pain**	8.1	7.2	7.9
Bone pain	5.1	3.3	1.0
Neck pain	5.1	6.6	5.0
Arthritis	4.0	2.2	1.5
Joint stiffness	3.5	1.1	2.0
Joint swelling	3.0	0.6	0.0
Flank pain	2.0	0.6	0.0
Pain in jaw	2.0	3.9	2.5
General disorders and administration site conditions			
Pain	24.2	14.9	3.5
Pyrexia	21.7	21.0	4.5
Chills	18.2	18.2	3.0
Fatigue	14.6	9.9	4.0
Asthenia	6.1	2.8	1.0
Peripheral edema	5.6	3.9	3.5
Non-cardiac chest pain	3.5	7.7	3.0
Influenza like illness	1.5	3.3	2.0
Malaise	1.0	2.2	0.5

* Combined abdominal pain, abdominal pain upper, and abdominal pain lower as one ADR
** Combined musculoskeletal pain and musculoskeletal chest pain as one ADR

Ocular Adverse Events

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the osteoporosis prevention trial, 4 (1.1%) patients treated with Reclast and 0 (0%) patients treated with placebo developed iritis/uveitis.

Acute Phase Reaction

In patients given Reclast at randomization and placebo at Month 12, Reclast was associated with signs and symptoms of an acute phase reaction: myalgia (20.4%), fever (19.3%), chills (18.2%), pain (13.8%), headache (13.3%), fatigue (8.3%), arthralgia (6.1%), pain in extremity (3.9%), influenza-like illness (3.3%), and back pain (1.7%), which occurred within the first 3 days following the dose of Reclast. The majority of these symptoms were mild to moderate and resolved within 3 days of the event onset but resolution could take up to 7-14 days.

Osteoporosis in Men

The safety of Reclast in men with osteoporosis or osteoporosis secondary to hypogonadism was assessed in a two year randomized, multicenter, double-blind, active controlled group study of 302 men aged 25-86 years. One hundred fifty three (153) patients were exposed to Reclast administered once annually with a 5 mg dose in 100 mL infused over 15 minutes for up to a total of two doses, and 148 patients were exposed to a commercially-available oral weekly bisphosphonate (active control) for up to two years. All participants received 1000 mg of elemental calcium plus 800 to 1000 IU of vitamin D supplementation per day.

The incidence of all-cause mortality (one in each group) and serious adverse events were similar between the Reclast and active control treatment groups. The percentage of patients experiencing at least one adverse event was comparable between the Reclast and active control groups, with the exception of a higher incidence of post-dose symptoms in the Reclast group that occurred within 3 days after infusion. The overall safety and tolerability of Reclast was similar to the active control.

Adverse reactions reported in at least 2% of men with osteoporosis and more frequently in the Reclast-treated patients than the active control-treated patients and either (1) not reported in the postmenopausal osteoporosis treatment trial or (2) reported more frequently in the trial of osteoporosis in men are presented in Table 3. Therefore, Table 3 should be viewed in conjunction with Table 1.

Table 3: Adverse Reactions Occurring in ≥ 2% of Men with Osteoporosis and More Frequently in the Reclast-Treated Patients than the Active Control-Treated Patients and either (1) Not Reported in the Postmenopausal Osteoporosis Treatment Trial or (2) Reported More Frequently in this Trial

System Organ Class	5 mg IV Reclast once per year % (N=153)	Active Control once weekly % (N=148)
Nervous System Disorders		
Headache	15.0	6.1
Lethargy	3.3	1.4
Eye Disorders		
Eye pain	2.0	0.0
Cardiac Disorders		
Atrial fibrillation	3.3	2.0
Palpitations	2.6	0.0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	6.5	4.7
Abdominal pain*	7.9	4.1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	2.6	2.0
Musculoskeletal, Connective Tissue and Bone Disorders		
Myalgia	19.6	6.8
Musculoskeletal pain**	12.4	10.8
Musculoskeletal stiffness	4.6	0.0
Renal and Urinary Disorders		
Blood creatinine increased	2.0	0.7
General Disorders and Administrative Site Conditions		
Fatigue	17.6	6.1
Pain	11.8	4.1
Chills	9.8	2.7
Influenza like illness	9.2	2.0
Malaise	7.2	0.7
Acute phase reaction	3.9	0.0
Investigations		
C-reactive protein increased	4.6	1.4

* Combined abdominal pain, abdominal pain upper, and abdominal pain lower as one ADR
** Combined musculoskeletal pain and musculoskeletal chest pain as one ADR

Renal Impairment

Creatinine clearance was measured annually prior to dosing and changes in long-term renal function over 24 months were comparable in the Reclast and active control groups [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

Reclast was associated with signs and symptoms of an acute phase reaction: myalgia (17.1%), fever (15.7%), fatigue (12.4%), arthralgia (11.1%), pain (10.5%), chills (9.8%), headache (9.8%), influenza-like illness (8.5%), malaise (5.2%), and back pain (3.3%), which occurred within the first 3 days following the dose of Reclast. The majority of these symptoms were mild to moderate and resolved within 3 days of the event onset but resolution could take up to 7-14 days. The incidence of these symptoms decreased with subsequent doses of Reclast.

Atrial Fibrillation

The incidence of all atrial fibrillation adverse events in the Reclast treatment group was 3.3% (5 out of 153) compared to 2.0% (3 out of 148) in the active control group. However, there were no patients with adjudicated serious adverse events of atrial fibrillation in the Reclast treatment group.

Laboratory Findings

There were no patients who had treatment emergent serum calcium levels below 7.5 mg/dL.

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Injection Site Reactions

There were 4 patients (2.6%) on Reclast vs. 2 patients (1.4%) on active control with local site reactions.

Osteonecrosis of the Jaw

In this trial there were no cases of osteonecrosis of the jaw [*see Warnings and Precautions (5.4)*].

Glucocorticoid-Induced Osteoporosis

The safety of Reclast in men and women in the treatment and prevention of glucocorticoid-induced osteoporosis was assessed in a randomized, multicenter, double-blind, active controlled, stratified study of 833 men and women aged 18-85 years treated with ≥ 7.5 mg/day oral prednisone (or equivalent). Patients were stratified according to the duration of their pre-study corticosteroid therapy: ≤ 3 months prior to randomization (prevention subpopulation), and > 3 months prior to randomization (treatment subpopulation).

The duration of the trial was one year with 416 patients exposed to Reclast administered once as a single 5 mg dose in 100 mL infused over 15 minutes, and 417 patients exposed to a commercially-available oral daily bisphosphonate (active control) for one year. All participants received 1000 mg of elemental calcium plus 400 to 1000 IU of vitamin D supplementation per day.

The incidence of all–cause mortality was similar between treatment groups: 0.9% in the Reclast group and 0.7% in the active control group. The incidence of serious adverse events was similar between the Reclast treatment and prevention groups, 18.4% and 18.1%, respectively, and the active control treatment and prevention groups, 19.8% and 16.0%, respectively. The percentage of subjects who withdrew from the study due to adverse events was 2.2% in the Reclast group vs. 1.4% in the active control group. The overall safety and tolerability were similar between Reclast and active control groups with the exception of a higher incidence of post-dose symptoms in the Reclast group that occurred within 3 days after infusion. The overall safety and tolerability profile of Reclast in glucocorticoid-induced osteoporosis was similar to the adverse events reported in the Reclast postmenopausal osteoporosis clinical trial.

Adverse reactions reported in at least 2% of patients that were either not reported in the postmenopausal osteoporosis treatment trial or reported more frequently in the treatment and prevention of glucocorticoid-induced osteoporosis trial included the following: abdominal pain (Reclast 7.5%; active control 5.0%), and musculoskeletal pain (Reclast 3.1%; active control 1.7%). Other musculoskeletal events included back pain (Reclast 4.3%, active control 6.2%), bone pain (Reclast 3.1%, active control 2.2%), and pain in the extremity (Reclast 3.1%, active control 1.2%). In addition, the following adverse events occurred more frequently than in the postmenopausal osteoporosis trial: nausea (Reclast 9.6%; active control 8.4%), and dyspepsia (Reclast 5.5%; active control 4.3%).

Renal Impairment

Renal function measured prior to dosing and at the end of the 12 month study was comparable in the Reclast and active control groups [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

Reclast was associated with signs and symptoms of a transient acute phase reaction that was similar to that seen in the Reclast postmenopausal osteoporosis clinical trial.

Atrial Fibrillation

The incidence of atrial fibrillation adverse events was 0.7% (3 of 416) in the Reclast group compared to no adverse events in the active control group. All subjects had a prior history of atrial fibrillation and no cases were adjudicated as serious adverse events. One patient had atrial flutter in the active control group.

Laboratory Findings

There were no patients who had treatment emergent serum calcium levels below 7.5 mg/dL.

Injection Site Reactions

There were no local reactions at the infusion site.

Osteonecrosis of the Jaw

In this trial there were no cases of osteonecrosis of the jaw [*see Warnings and Precautions (5.4)*].

Paget's Disease of Bone

In the Paget's disease trials, two 6-month, double-blind, comparative, multinational studies of 349 men and women aged > 30 years with moderate to severe disease and with confirmed Paget's disease of bone, 177 patients were exposed to Reclast and 172 patients exposed to risedronate. Reclast was administered once as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. Risedronate was given as an oral daily dose of 30 mg for 2 months.

The incidence of serious adverse events was 5.1% in the Reclast group and 6.4% in the risedronate group. The percentage of patients who withdrew from the study due to adverse events was 1.7% and 1.2% for the Reclast and risedronate groups, respectively.

Adverse reactions occurring in at least 2% of the Paget's patients receiving Reclast (single 5 mg IV infusion) or risedronate (30 mg oral daily dose for 2 months) over a 6-month study period are listed by system organ class in Table 4.

Table 4. Adverse Reactions Reported in at Least 2% of Paget's Patients Receiving Reclast (Single 5 mg IV Infusion) or Risedronate (Oral 30 mg Daily for 2 Months) Over a 6-Month Follow-Up Period

System Organ Class	5 mg IV Reclast % (N = 177)	30 mg/day x 2 Months risedronate % (N = 172)
Infections and Infestations		
Influenza	7	5
Metabolism and Nutrition Disorders		
Hypocalcemia	3	1
Anorexia	2	2
Nervous System Disorders		
Headache	11	10
Dizziness	9	4
Lethargy	5	1
Paresthesia	2	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	5	1
Gastrointestinal Disorders		
Nausea	9	6
Diarrhea	6	6
Constipation	6	5
Dyspepsia	5	4
Abdominal Distension	2	1
Abdominal Pain	2	2
Vomiting	2	2
Abdominal Pain Upper	1	2
Skin and Subcutaneous Tissue Disorders		
Rash	3	2
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgia	9	11
Bone Pain	9	5
Myalgia	7	4
Back Pain	4	7
Musculoskeletal Stiffness	2	1
General Disorders and Administrative Site Conditions		
Influenza-like Illness	11	6
Pyrexia	9	2
Fatigue	8	4
Rigors	8	1
Pain	5	4
Peripheral Edema	3	1
Asthenia	2	1

Laboratory Findings

In the Paget's disease trials, early, transient decreases in serum calcium and phosphate levels were observed. Approximately 21% of patients had serum calcium levels <8.4 mg/dL 9-11 days following Reclast administration.

Renal Impairment

In clinical trials in Paget's disease there were no cases of renal deterioration following a single 5 mg 15-minute infusion [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

The signs and symptoms of acute phase reaction (influenza-like illness, pyrexia, myalgia, arthralgia, and bone pain) were reported in 25% of patients in the Reclast-treated group compared to 8% in the risedronate-treated group. Symptoms usually occur within the first 3 days following Reclast administration. The majority of these symptoms resolved within 4 days of onset.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported with zoledronic acid [*see Warnings and Precautions (5.4)*].

6.2 Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post approval use of Reclast:

Acute Phase Reactions

Fever, headache, flu-like symptoms, nausea, vomiting, diarrhea, arthralgia, and myalgia. Symptoms may be significant and lead to dehydration.

Acute Renal Failure

Cases of acute renal failure requiring hospitalization and/or dialysis or with a fatal outcome have been rarely reported. Increased serum creatinine was reported in patients with 1) underlying renal disease, 2) dehydration secondary to fever, sepsis, gastrointestinal losses, or diuretic therapy, or 3) other risk factors such as advanced age, or concomitant nephrotoxic drugs in the post-infusion period. Transient rise in serum creatinine can be correctable with intravenous fluids;

Allergic Reactions

There have been rare reports of allergic reaction with intravenous zoledronic acid including urticaria, angioedema, and bronchoconstriction. Rare cases of anaphylactic reaction/shock have also been reported.

Hypocalcemia

Rare cases of hypocalcemia have been reported.

Osteonecrosis of the Jaw

Rare cases of osteonecrosis of the jaw have been reported.

Ocular Adverse Events

Rare cases of the following events have been reported: conjunctivitis, iritis, iridocyclitis, uveitis, episcleritis, scleritis and orbital inflammation/edema.

Other

Rare cases of hypotension in patients with underlying risk factors have been reported.

7 DRUG INTERACTIONS

No *in vivo* drug interaction studies have been performed for Reclast. *In vitro* and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro* mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

7.1 Aminoglycosides

Caution is advised when bisphosphonates, including zoledronic acid, are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in zoledronic acid clinical trials.

7.2 Loop Diuretics

Caution should also be exercised when Reclast is used in combination with loop diuretics due to an increased risk of hypocalcemia.

7.3 Nephrotoxic Drugs

Caution is indicated when Reclast is used with other potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs.

7.4 Drugs Primarily Excreted by the Kidney

Renal impairment has been observed following the administration of zoledronic acid in patients with pre-existing renal compromise or other risk factors [*see Warnings and Precautions (5.3)*]. In patients with renal impairment, the exposure to concomitant medications that are primarily renally excreted (e.g., digoxin) may increase. Consider monitoring serum creatinine in patients at risk for renal impairment who are taking concomitant medications that are primarily excreted by the kidney.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.6)*].

RECLAST SHOULD NOT BE USED DURING PREGNANCY. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving Reclast.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception space, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

In female rats given daily subcutaneous doses of zoledronic acid beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased at approximately ≥ 0.3 times the anticipated human systemic exposure following a 5 mg intravenous dose (based on an AUC comparison). Adverse maternal effects were observed in all dose groups at ≥ 0.1 times the human systemic exposure following a 5 mg intravenous dose (based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality was considered related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given daily subcutaneous dose of zoledronic acid during gestation, adverse fetal effects were observed at about 2 and 4 times human systemic exposure following a 5 mg intravenous dose (based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations.

In pregnant rabbits given daily subcutaneous doses of zoledronic acid during gestation at doses ≤ 0.4 times the anticipated human systemic exposure following a 5 mg intravenous dose (based on a mg/m^2 comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥ 0.04 times the human 5 mg intravenous dose, based on a mg/m^2 comparison). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia [*see Nonclinical Toxicology (13.3)*].

8.3 Nursing Mothers

It is not known whether Reclast is excreted in human milk. Because many drugs are excreted in human milk, and because Reclast binds to bone long-term, Reclast should not be administered to a nursing woman.

8.4 Pediatric Use

Reclast is not indicated for use in children.

The safety and effectiveness of zoledronic acid was studied in a one-year active controlled trial of 152 pediatric subjects (74 receiving zoledronic acid). The enrolled population was subjects with severe osteogenesis imperfecta, aged 1-17 years, 55% male, 84% Caucasian, with a mean lumbar spine BMD of 0.431 gm/cm^2, which is 2.7 standard deviations below the mean for age-matched controls (BMD Z-score of -2.7). At one year, increases in BMD were observed in the zoledronic acid treatment group. However, changes in BMD in individual patients with severe osteogenesis imperfecta did

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not necessarily correlate with the risk for fracture or the incidence or severity of chronic bone pain. The adverse events observed with zoledronic acid use in children did not raise any new safety findings beyond those previously seen in adults treated for Paget's disease of bone and treatment of osteoporosis including osteonecrosis of the jaw (ONJ) and renal impairment. However, adverse reactions seen more commonly in pediatric patients included pyrexia (61%), arthralgia (26%), hypocalcemia (22%) and headache (22%). These reactions, excluding arthralgia, occurred most frequently within three days after the first infusion and became less common with repeat dosing. No cases of ONJ or renal impairment were observed in this study. Because of long-term retention in bone, Reclast should only be used in children if the potential benefit outweighs the potential risk.

Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteogenesis imperfecta (4 in the age group of 3-8 years and 6 in the age group of 9-17 years) infused with 0.05 mg/kg dose over 30 minutes. Mean C_{max} and $AUC_{(0\text{-last})}$ was 167 ng/mL and 220 ng.h/mL respectively. The plasma concentration time profile of zoledronic acid in pediatric patients represent a multi-exponential decline, as observed in adult cancer patients at an approximately equivalent mg/kg dose.

8.5 Geriatric Use

The combined osteoporosis trials included 4863 Reclast-treated patients who were at least 65 years of age, while 2101 patients were at least 75 years old. No overall differences in efficacy or safety were observed between patients under 75 years of age with those at least 75 years of age, except that the acute phase reactions occurred less frequently in the older patients.

Of the patients receiving Reclast in the osteoporosis study in men, glucocorticoid-induced osteoporosis, and Paget's disease studies, 83, 116, and 132 patients, respectively were 65 years of age or over, while 24, 29, and 68 patients, respectively were at least 75 years of age.

However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

8.6 Renal Impairment

Reclast is contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment. There are no safety or efficacy data to support the adjustment of the Reclast dose based on baseline renal function. Therefore, no dosage adjustment is required in patients with a creatinine clearance of ≥ 35 mL/min [*see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)*]. Risk of acute renal failure may increase with underlying renal disease and dehydration secondary to fever, sepsis, gastrointestinal losses, diuretic therapy, advanced age, etc. [*see Post-Marketing Experience (6.2)*].

8.7 Hepatic Impairment

Reclast is not metabolized in the liver. No clinical data are available for use of Reclast in patients with hepatic impairment.

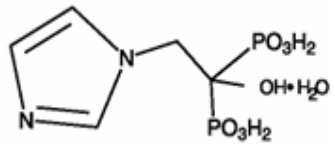
10 OVERDOSAGE

Clinical experience with acute overdosage of zoledronic acid (Reclast) solution for intravenous infusion is limited. Patients who have received doses higher than those recommended should be carefully monitored. Overdosage may cause clinically significant renal impairment, hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

Single doses of Reclast should not exceed 5 mg and the duration of the intravenous infusion should be no less than 15 minutes [*see Dosage and Administration (2)*].

11 DESCRIPTION

Reclast contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is:



Zoledronic acid monohydrate is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \bullet H_2O$ and a molar mass of 290.1 g/Mol. Zoledronic acid monohydrate is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of the Reclast solution for infusion is approximately 6.0 – 7.0.

Reclast Injection is available as a sterile solution in bottles for intravenous infusion. One bottle with 100 mL solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis.

Inactive Ingredients: 4950 mg of mannitol, USP; and 30 mg of sodium citrate, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Reclast is a bisphosphonate and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid rapidly partitions to bone and localizes preferentially at sites of high bone turnover. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity to bone mineral.

12.2 Pharmacodynamics

In the osteoporosis treatment trial, the effect of Reclast treatment on markers of bone resorption (serum beta-C-telopeptides [b-CTx]) and bone formation (bone specific alkaline phosphatase [BSAP], serum N-terminal propeptide of type I collagen [P1NP]) was evaluated in patients (subsets ranging from 517 to 1246 patients) at periodic intervals. Treatment with a 5 mg annual dose of Reclast reduces bone turnover markers to the pre-menopausal range with an approximate 55% reduction in b-CTx, a 29% reduction in BSAP and a 52 % reduction in P1NP over 36 months. There was no progressive reduction of bone turnover markers with repeated annual dosing.

12.3 Pharmacokinetics

Pharmacokinetic data in patients with osteoporosis and Paget's disease of bone are not available.

***Distribution*:** Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hour and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve ($AUC_{0\text{-}24h}$) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0\text{-}24h}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro* mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL.

Metabolism: Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, < 3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion: In 64 patients with cancer and bone metastases on average (± SD) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic

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circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL vs. 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs. 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Specific Populations

Pediatrics: Reclast is not indicated for use in children [*see Pediatric Use (8.4)*].

Geriatrics: The pharmacokinetics of zoledronic acid was not affected by age in patients with cancer and bone metastases whose age ranged from 38 years to 84 years.

Race: The pharmacokinetics of zoledronic acid was not affected by race in patients with cancer and bone metastases.

Hepatic Impairment: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Impairment: The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately-impaired renal function. Compared to patients with creatinine clearance > 80 mL/min (N=37), patients with creatinine clearance = 50-80 mL/min (N=15) showed an average increase in plasma AUC of 15%, whereas patients with creatinine clearance = 30-50 mL/min (N=11) showed an average increase in plasma AUC of 43%. No dosage adjustment is required in patients with a creatinine clearance of ≥ 35 mL/min. Reclast is contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment due to an increased risk of renal failure [*see Contraindications (4.2), Warnings and Precautions (5.3), Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given daily oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥0.002 times the human intravenous dose of 5 mg, based on a mg/m^2 comparison). Rats were given daily oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤ 0.1 times the human intravenous dose of 5 mg, based on a mg/m^2 comparison).

Mutagenesis: Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

Impairment of Fertility: Female rats were given daily subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (equivalent to human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group and high-dose group (0.3 to 1 times human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

13.2 Animal Pharmacology

Bone Safety Studies: Zoledronic acid is a potent inhibitor of osteoclastic bone resorption. In the ovariectomized rat, single IV doses of zoledronic acid of 4-500 μg/kg (<0.1 to 3.5 times human exposure at the 5 mg intravenous dose, based on a mg/m^2 comparison) suppressed bone turnover and protected against trabecular bone loss, cortical thinning and the reduction in vertebral and femoral bone strength in a dose-dependent manner. At a dose equivalent to human exposure at the 5 mg intravenous dose, the effect persisted for 8 months, which corresponds to approximately 8 remodeling cycles or 3 years in humans.

In ovariectomized rats and monkeys, weekly treatment with zoledronic acid dose-dependently suppressed bone turnover and prevented the decrease in cancellous and cortical BMD and bone strength, at yearly cumulative doses up to 3.5 times the intravenous human dose of 5 mg, based on a mg/m^2 comparison. Bone tissue was normal and there was no evidence of a mineralization defect, no accumulation of osteoid, and no woven bone.

13.3 Reproductive and Developmental Toxicology

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥0.3 times the anticipated human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (≥0.1 times the human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality was considered related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given daily subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg during gestation, adverse fetal effects were observed in the mid- and high-dose groups (about 2 and 4 times human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (about 1.2 times the anticipated human systemic exposure, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (at doses ≤ 0.4 times the anticipated human systemic exposure following a 5 mg intravenous dose, based on a mg/m^2 comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥ 0.04 times the human 5 mg intravenous dose, based on a mg/m^2 comparison). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

14 CLINICAL STUDIES

14.1 Treatment of Postmenopausal Osteoporosis

Study 1: The efficacy and safety of Reclast in the treatment of postmenopausal osteoporosis was demonstrated in Study 1, a randomized, double-blind, placebo-controlled, multinational study of 7736 women aged 65-89 years (mean age of 73) with either: a femoral neck BMD T-score less than or equal to -1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score less than or equal to -2.5 with or without evidence of an existing vertebral fracture(s). Women were stratified into two groups: Stratum I: no concomitant use of osteoporosis therapy or Stratum II: baseline concomitant use of osteoporosis therapies which included calcitonin, raloxifene, tamoxifen, and hormone replacement therapy, but excluded other bisphosphonates.

Women enrolled in Stratum I (n=5661) were evaluated annually for incidence of vertebral fractures. All women (Strata I and II) were evaluated for the incidence of hip and other clinical fractures. Reclast was administered once a year for three consecutive years, as a single 5 mg dose in 100 mL solution infused over at least 15 minutes, for a total of three doses. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplementation per day.

The two primary efficacy variables were the incidence of morphometric vertebral fractures at 3 years and the incidence of hip fractures over a median duration of 3 years. 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.

Effect on Vertebral Fractures

Reclast significantly decreased the incidence of new vertebral fractures at one, two, and three years as shown in Table 5.

Reference ID: 3008875

Table 5. Proportion of Patients with New Morphometric Vertebral Fractures

Outcome	Reclast (%)	Placebo (%)	Absolute Reduction in Fracture Incidence % (95% CI)	Relative Reduction in Fracture Incidence % (95% CI)
At least one new vertebral fracture (0–1 year)	1.5	3.7	2.2 (1.4, 3.1)	60 (43, 72)*
At least one new vertebral fracture (0–2 years)	2.2	7.7	5.5 (4.4, 6.6)	71 (62, 78)*
At least one new vertebral fracture (0–3 years)	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)*

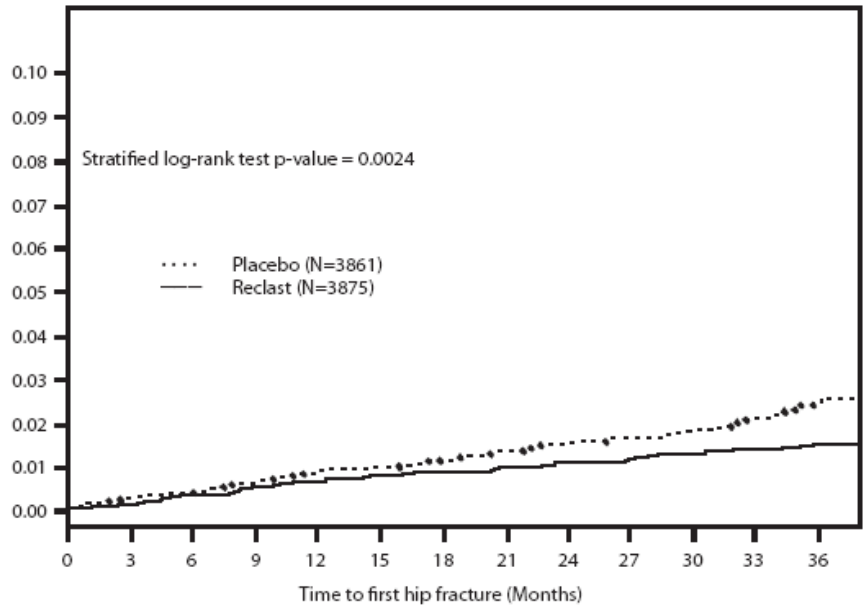
* $p < 0.0001$

The reductions in vertebral fractures over three years were consistent (including new/worsening and multiple vertebral fractures) and significantly greater than placebo regardless of age, geographical region, baseline body mass index, number of baseline vertebral fractures, femoral neck BMD T-score, or prior bisphosphonate usage.

Effect on Hip Fracture over 3 years

Reclast demonstrated a 1.1% absolute reduction and 41% relative reduction in the risk of hip fractures over a median duration of follow-up of 3 years. The hip fracture event rate was 1.4% for Reclast-treated patients compared to 2.5% for placebo-treated patients.

Figure 1. Cumulative Incidence of Hip Fracture Over 3 Years



The reductions in hip fractures over three years were greater for Reclast than placebo regardless of femoral neck BMD T-score.

Effect on All Clinical Fractures

Reclast demonstrated superiority to placebo in reducing the incidence of all clinical fractures, clinical (symptomatic) vertebral and non-vertebral fractures (excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures). All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 6.

Reference ID: 3008875

Table 6. Between–Treatment Comparisons of the Incidence of Clinical Fracture Variables Over 3 Years

Outcome	Reclast (N= 3875) Event Rate n (%)+	Placebo (N= 3861) Event Rate n (%)+	Absolute Reduction in Fracture Incidence % (95% CI)+	Relative Risk Reduction in Fracture Incidence % (95% CI)
Any clinical fracture (1)	308 (8.4)	456 (12.8)	4.4 (3.0, 5.8)	33 (23, 42)**
Clinical vertebral fracture (2)	19 (0.5)	84 (2.6)	2.1 (1.5, 2.7)	77 (63, 86)**
Non-vertebral fracture (3)	292 (8.0)	388 (10.7)	2.7 (1.4, 4.0)	25 (13, 36)*

*p-value < 0.001, **p-value <0.0001

+ Event rates based on Kaplan-Meier estimates at 36 months

(1) Excluding finger, toe, and facial fractures

(2) Includes clinical thoracic and clinical lumbar vertebral fractures

(3) Excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures

Effect on Bone Mineral Density (BMD)

Reclast significantly increased BMD at the lumbar spine, total hip and femoral neck, relative to treatment with placebo at time points 12, 24, and 36 months. Treatment with Reclast resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, and 5.1% at the femoral neck, over 3 years as compared to placebo.

Bone Histology

Bone biopsy specimens were obtained between Months 33 and 36 from 82 postmenopausal patients with osteoporosis treated with 3 annual doses of Reclast. Of the biopsies obtained, 81 were adequate for qualitative histomorphometry assessment, 59 were adequate for partial quantitative histomorphometry assessment, and 38 were adequate for full quantitative histomorphometry assessment. Micro CT analysis was performed on 76 specimens. Qualitative, quantitative and micro CT assessments showed bone of normal architecture and quality without mineralization defects.

Effect on Height

In the 3-year osteoporosis study, standing height was measured annually using a stadiometer. The Reclast group revealed less height loss compared to placebo (4.2 mm vs. 7.0 mm, respectively [p<0.001]).

Study 2: The efficacy and safety of Reclast in the treatment of patients with osteoporosis who suffered a recent low-trauma hip fracture was demonstrated in Study 2, a randomized, double-blind, placebo-controlled, multinational endpoint study of 2127 men and women aged 50-95 years (mean age of 74.5). Concomitant osteoporosis therapies excluding other bisphosphonates and parathyroid hormone were allowed. Reclast was administered once a year as a single 5 mg dose in 100 mL solution, infused over at least 15 minutes. The study continued until at least 211 patients had confirmed clinical fractures in the study population. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 IU orally or IM) was given to patients and they were started on 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day for at least 14 days prior to the study drug infusions. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Reclast significantly reduced the incidence of any clinical fracture by 35%. There was also a 46% reduction in the risk of a clinical vertebral fracture (Table 7).

Reference ID: 3008875

Table 7. Between-Treatment Comparisons of the Incidence of Key Clinical Fracture Variables

Outcome	Reclast (N=1065) Event Rate n (%)+	Placebo (N=1062) Event Rate n (%)+	Absolute Reduction in Fracture Incidence % (95% CI)+	Relative Risk Reduction in Fracture Incidence % (95% CI)
Any clinical fracture (1)	92 (8.6)	139 (13.9)	5.3 (2.3, 8.3)	35 (16, 50)**
Clinical vertebral fracture (2)	21 (1.7)	39 (3.8)	2.1 (0.5, 3.7)	46 (8, 68)*

*p-value <0.05, **p-value <0.005
+ Event rates based on Kaplan-Meier estimates at 24 months
(1) Excluding finger, toe and facial fractures
(2) Including clinical thoracic and clinical lumbar vertebral fractures

Effect on Bone Mineral Density (BMD)

Reclast significantly increased BMD relative to placebo at the hip and femoral neck at all timepoints (12, 24, and 36 months). Treatment with Reclast resulted in a 6.4% increase in BMD at the total hip and a 4.3% increase at the femoral neck over 36 months as compared to placebo.

14.2 Prevention of Postmenopausal Osteoporosis

The efficacy and safety of Reclast in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged ≥ 45 years, who were stratified by years since menopause: Stratum I women < 5 years from menopause (n=224); Stratum II women ≥ 5 years from menopause (n=357). Patients within Stratum I and II were randomized to one of three treatment groups: (1) Reclast given at randomization and at Month 12 (n=77) in Stratum I and (n=121) in Stratum II; (2) Reclast given at randomization and placebo at Month 12 (n=70) in Stratum I and (n=111) in Stratum II; and (3) Placebo given at randomization and Month 12 (n=202). Reclast was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day. The primary efficacy variable was the percent change of BMD at 24 Months relative to baseline.

Effect on Bone Mineral Density (BMD)

Reclast significantly increased lumbar spine BMD relative to placebo at Month 24 across both strata. Reclast given once at randomization (and placebo given at Month 12) resulted in 4.0% increase in BMD in Stratum I patients and 4.8% increase in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.2% decrease in BMD in Stratum I patients and 0.7% decrease in BMD in Stratum II patients over 24 months. Therefore, Reclast given once at randomization (and placebo given at Month 12) resulted in a 6.3% increase in BMD in Stratum I patients and 5.4% increase in Stratum II patients over 24 months as compared to placebo (both p<0.0001).

Reclast also significantly increased total hip BMD relative to placebo at Month 24 across both strata. Reclast given once at randomization (and placebo given at Month 12) resulted in 2.6% increase in BMD in Stratum I patients and 2.1% in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.1% decrease in BMD in Stratum I patients and 1.0% decrease in BMD in Stratum II patients over 24 months. Therefore, Reclast given once at randomization (and placebo given at Month 12) resulted in a 4.7% increase in BMD in Stratum I patients and 3.2% increase in Stratum II patients over 24 months as compared to placebo (both p<0.0001).

14.3 Osteoporosis in Men

The efficacy and safety of Reclast in men with osteoporosis or significant osteoporosis secondary to hypogonadism, was assessed in a randomized, multicenter, double-blind, active controlled, study of 302 men aged 25-86 years (mean age of 64). The duration of the trial was two years. Patients were randomized to either Reclast which was administered once annually as a 5 mg dose in 100 mL infused over 15 minutes for a total of up to two doses, or to an oral weekly bisphosphonate (active control) for up to two years. All participants received 1000 mg of elemental calcium plus 800 to 1000 IU of vitamin D supplementation per day.

Effect on Bone Mineral Density (BMD)

An annual infusion of Reclast was non-inferior to the oral weekly bisphosphonate active control based on the percentage change in lumbar spine BMD at Month 24 relative to baseline (Reclast: 6.1% increase; active control: 6.2% increase).

Reference ID: 3008875

14.4 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The efficacy and safety of Reclast to prevent and treat glucocorticoid-induced osteoporosis (GIO) was assessed in a randomized, multicenter, double-blind, stratified, active controlled study of 833 men and women aged 18-85 years (mean age of 54.4 years) treated with ≥ 7.5 mg/day oral prednisone (or equivalent). Patients were stratified according to the duration of their pre-study corticosteroid therapy: ≤ 3 months prior to randomization (prevention subpopulation), and > 3 months prior to randomization (treatment subpopulation). The duration of the trial was one year. Patients were randomized to either Reclast which was administered once as a 5 mg dose in 100 mL infused over 15 minutes, or to an oral daily bisphosphonate (active control) for one year. All participants received 1000 mg of elemental calcium plus 400 to 1000 IU of vitamin D supplementation per day.

Effect on Bone Mineral Density (BMD)

In the GIO treatment subpopulation, Reclast demonstrated a significant mean increase in lumbar spine BMD compared to the active control at one year (Reclast 4.1%, active control 2.7%) with a treatment difference of 1.4% ($p<0.001$). In the GIO prevention subpopulation, Reclast demonstrated a significant mean increase in lumbar spine BMD compared to active control at one year (Reclast 2.6%, active control 0.6%) with a treatment difference of 2.0% ($p<0.001$).

Bone Histology

Bone biopsy specimens were obtained from 23 patients (12 in the Reclast treatment group and 11 in the active control treatment group) at Month 12 treated with an annual dose of Reclast or daily oral active control. Qualitative assessments showed bone of normal architecture and quality without mineralization defects. Apparent reductions in activation frequency and remodeling rates were seen when compared with the histomorphometry results seen with Reclast in the postmenopausal osteoporosis population. The long-term consequences of this degree of suppression of bone remodeling in glucocorticoid-treated patients is unknown.

14.5 Treatment of Paget's Disease of Bone

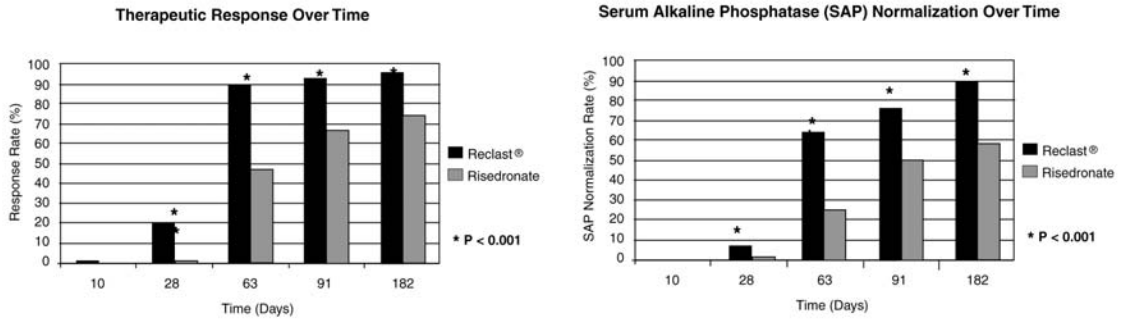
Reclast was studied in male and female patients with moderate to severe Paget's disease of bone, defined as serum alkaline phosphatase level at least twice the upper limit of the age-specific normal reference range at the time of study entry. Diagnosis was confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg Reclast vs. oral daily doses of 30 mg risedronate for 2 months was demonstrated in two identically designed 6-month randomized, double blind trials. The mean age of patients in the two trials was 70. Ninety-three percent (93%) of patients were Caucasian. Therapeutic response was defined as either normalization of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. SAP excess was defined as the difference between the measured level and midpoint of normal range.

In both trials Reclast demonstrated a superior and more rapid therapeutic response compared with risedronate and returned more patients to normal levels of bone turnover, as evidenced by biochemical markers of formation (SAP, serum N-terminal propeptide of type I collagen [P1NP]) and resorption (serum CTx 1 [cross-linked C-telopeptides of type I collagen] and urine α-CTx).

The 6-month combined data from both trials showed that 96% (169/176) of Reclast-treated patients achieved a therapeutic response as compared with 74% (127/171) of patients treated with risedronate. Most Reclast patients achieved a therapeutic response by the Day 63 visit. In addition, at 6 months, 89% (156/176) of Reclast-treated patients achieved normalization of SAP levels, compared to 58% (99/171) of patients treated with risedronate ($p<0.0001$) (see Figure 2).

Figure 2. Therapeutic Response/Serum Alkaline Phosphatase (SAP) Normalization Over Time



The therapeutic response to Reclast was similar across demographic and disease-severity groups defined by gender, age, previous bisphosphonate use, and disease severity. At 6 months, the percentage of Reclast-treated patients who achieved therapeutic response was 97% and 95%, respectively, in each of the baseline disease severity subgroups (baseline SAP < 3xULN, ≥ 3xULN) compared to 75% and 74%, respectively, for the same disease severity subgroups of risedronate-treated patients.

In patients who had previously received treatment with oral bisphosphonates, therapeutic response rates were 96% and 55% for Reclast and risedronate, respectively. The comparatively low risedronate response was due to the low response rate (7/23, 30%) in patients previously treated with risedronate. In patients naïve to previous treatment, a greater therapeutic response was also observed with Reclast (98%) relative to risedronate (86%). In patients with symptomatic pain at screening, therapeutic response rates were 94% and 70% for Reclast and risedronate respectively. For patients without pain at screening, therapeutic response rates were 100% and 82% for Reclast and risedronate respectively.

Bone histology was evaluated in 7 patients with Paget's disease 6 months after being treated with Reclast 5 mg. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodeling and no evidence of mineralization defect.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each bottle contains 5 mg/100 mL. NDC 0078-0435-61

Handling

After opening the solution, it is stable for 24 hours at 2°C–8°C (36°F-46°F).

If refrigerated, allow the refrigerated solution to reach room temperature before administration.

Storage

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

Information for Patients

Patients should be made aware that Reclast contains the same active ingredient (zoledronic acid) found in Zometa®, and that patients being treated with Zometa should not be treated with Reclast.

Reclast is contraindicated in patients with creatinine clearance < 35 ml/min. [*See Contraindications (4.2)*].

Before being given Reclast, patients should tell their doctor if they have kidney problems and what medications they are taking.

Reclast should not be given if the patient is pregnant or plans to become pregnant, or if she is breast-feeding [*see Warnings and Precautions (5.6)*].

There have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates, including Reclast. Before being given Reclast, patients should tell their doctor if they are aspirin-sensitive.

If the patient had surgery to remove some or all of the parathyroid glands in their neck, or had sections of their intestine removed, or are unable to take calcium supplements they should tell their doctor.

Reclast is given as an infusion into a vein by a nurse or a doctor, and the infusion time must not be less than 15 minutes.

On the day of treatment the patient should eat and drink normally, which includes drinking at least 2 glasses of fluid such as water within a few hours prior to the infusion, as directed by their doctor, before receiving Reclast.

After getting Reclast it is strongly recommended patients with Paget's disease take calcium in divided doses (for example, 2 to 4 times a day) for a total of 1500 mg calcium a day to prevent low blood calcium levels. This is especially important for the two weeks after getting Reclast [*see Warnings and Precautions (5.2)*].

Adequate calcium and vitamin D intake is important in patients with osteoporosis and the current recommended daily intake of calcium is 1200 mg and vitamin D is 800 IU – 1000 IU daily. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels.

Patients should be aware of the most commonly associated side effects of therapy. Patients may experience one or more side effects that could include: fever, flu-like symptoms, myalgia, arthralgia, and headache. Most of these side effects occur within the first 3 days following the dose of Reclast. They usually resolve within 3 days of onset but may last for up to 7 to 14 days. Patients should consult their physician if they have questions or if these symptoms persist. The incidence of these symptoms decreased markedly with subsequent doses of Reclast.

Administration of acetaminophen following Reclast administration may reduce the incidence of these symptoms**.**

Physicians should inform their patients that there have been reports of persistent pain and/or a non-healing sore of the mouth or jaw, primarily in patients treated with bisphosphonates for other illnesses. If they experience these symptoms, they should inform their physician or dentist.

Severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Reclast. Consider withholding future Reclast treatment if severe symptoms develop.

Atypical femur fractures in patients on bisphosphonate therapy have been reported; patients with thigh or groin pain should be evaluated to rule out a femoral fracture.

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MEDICATION GUIDE

Reclast® (RE-clast)

(zoledronic acid)

Injection

Read the Medication Guide that comes with Reclast before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about Reclast.

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

You should not receive Reclast if you are already receiving Zometa. Both Reclast and Zometa contain zoledronic acid.

Reclast can cause serious side effects including:

1. Low calcium levels in your blood (hypocalcemia)
2. Severe kidney problems
3. Severe jaw bone problems (osteonecrosis)
4. Bone, joint or muscle pain
5. Unusual thigh bone fractures

1. **Low calcium levels in your blood (hypocalcemia)**.
Reclast may lower the calcium levels in your blood. If you have low blood calcium before you start taking Reclast, it may get worse during treatment. Your low blood calcium must be treated before you take Reclast. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take Reclast. Take calcium and vitamin D as your doctor tells you to.

2. **Severe kidney problems.**

Severe kidney problems may happen when you take Reclast. Severe kidney problems may lead to hospitalization or kidney dialysis and can be life-threatening. Your risk of kidney problems is higher if you:

- already have kidney problems
- take a diuretic or “water pill”
- do not have enough water in your body (dehydrated) before or after you receive Reclast
- are of advanced age since the risk increases as you get older
- take any medicines known to harm your kidneys

You should drink at least 2 glasses of fluid within a few hours before receiving Reclast to reduce the risk of kidney problems.

3. **Severe jaw bone problems (osteonecrosis).**
Severe jaw bone problems may happen when you take Reclast. Your doctor should examine your mouth before you start Reclast. Your doctor may tell you to see your dentist before you start Reclast. It is important for you to practice good mouth care during treatment with Reclast.

4. **Unusual thigh bone fractures.**
Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

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5. **Possible harm to your unborn baby.**
Reclast should not be used if you are pregnant. Tell your doctor right away if you are pregnant or plan to become pregnant. Reclast may harm your unborn baby.

6. **Bone, joint, or muscle pain**
Some people who take bisphosphonates develop severe bone, joint, or muscle pain.

Call your doctor right away if you have any of these side effects.

What is Reclast?

Reclast is a prescription medicine used to:

- Treat or prevent osteoporosis in women after menopause. Reclast helps reduce the chance of having a hip or spinal fracture (break).
- Increase bone mass in men with osteoporosis.
- Treat or prevent osteoporosis in either men or women who will be taking corticosteroid medicines for at least one year.
- Treat certain men and women who have Paget's disease of the bone.

It is not known how long Reclast works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if Reclast is still right for you.

Reclast is not for use in children.

Who should not take Reclast?

Do not take Reclast if you:

- Have low levels of calcium in your blood
- Have kidney problems
- Are allergic to zoledronic acid or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking Reclast?

Before you start Reclast, be sure to talk to your doctor if you:

- Have low blood calcium.
- Have kidney problems.
- Had parathyroid or thyroid surgery (glands in your neck).
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome) or have had parts of your intestine removed.
- Have asthma (wheezing) from taking aspirin.
- Plan to have dental surgery or teeth removed.
- Are pregnant, or plan to become pregnant. Reclast may harm your unborn baby. **Reclast should not be used if you are pregnant.**
- Are breastfeeding or plan to breastfeed. It is not known if Reclast passes into your milk and may harm your baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how Reclast works.

Especially tell your doctor if you are taking:

- An antibiotic. Certain antibiotic medicines called aminoglycosides may increase the effect of Reclast in lowering your blood calcium for a long period of time.
- A diuretic or "water pill".
- Non-steroidal anti-inflammatory medicines (NSAIDS).

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How will I receive Reclast?

- Your doctor will tell you how often you will receive Reclast.
- Reclast is given by infusion into your vein (intravenously). Your infusion should last at least 15 minutes.
- Before you receive Reclast, drink at least 2 glasses of fluid (such as water) within a few hours as directed by your doctor.
- You may eat before your treatment with Reclast.
- If you miss a dose of Reclast, call your doctor or healthcare provider to schedule your next dose.

What are the possible side effects of Reclast?

Reclast may cause serious side effects.

- See "**What is the most important information I should know about Reclast?"**

The most common side effects of Reclast included:

- Fever
- Pain in your bones, joints or muscles
- Pain in your arms and legs
- Headache
- Flu-like illness (fever, chills, bone, joint, or muscle pain, fatigue)
- Nausea
- Vomiting
- Diarrhea

Talk to your doctor about things you can do to help decrease some of these side effects that might happen with a Reclast infusion.

You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Reclast. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about safe and effective use of Reclast.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Reclast. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Reclast that is written for health professionals.

For more information, go to: www.RECLAST.com or call 1-866-732-5278.

What are the ingredients in Reclast?

Active ingredient: zoledronic acid monohydrate

Inactive ingredients: mannitol and sodium citrate.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Atelvia safely and effectively. See Full Prescribing Information for Atelvia.

Atelvia™ (risedronate sodium) delayed-release tablets
Initial U.S. Approval: 1998

RECENT MAJOR CHANGES

- Indications and Usage [(1.2) 01/2011]
- Warnings and Precautions [(5.6) 01/2011]

INDICATIONS AND USAGE

Atelvia is a bisphosphonate in a delayed-release formulation and is indicated for treatment of postmenopausal osteoporosis (1.1)
The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

DOSAGE AND ADMINISTRATION

Take Atelvia in the morning immediately following breakfast with at least 4 oz. of plain water. Do not lie down for 30 minutes after taking Atelvia (2)
One 35 mg delayed-release tablet once a week (2.1)

DOSAGE FORMS AND STRENGTHS

Delayed-release tablets: 35 mg (3)

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia (4, 5.2)
- Inability to stand or sit upright for at least 30 minutes (4, 5.2)
- Hypocalcemia (4, 5.3)
- Known hypersensitivity to any component of this product (4, 6.2)

WARNINGS AND PRECAUTIONS

- Atelvia and Actonel contain the same active ingredient. Patients receiving Actonel should not be treated with Atelvia (5.1)
- Severe irritation of the upper gastrointestinal (GI) mucosa can occur. Dosing instructions should be followed and caution should be used in patients with active upper GI disease. Discontinue use if new or worsening symptoms occur (5.2)
- Hypocalcemia may worsen and must be corrected prior to use (5.3)
- Osteonecrosis of the jaw has been reported rarely (5.4)
- Severe bone, joint, or muscle pain may occur. Consider discontinuing use if severe symptoms develop (5.5, 6.2)
- Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture.

ADVERSE REACTIONS

Most common adverse reactions (>5%) include: diarrhea, influenza, arthralgia, back pain, and abdominal pain (6.1)
Hypersensitivity reactions (angioedema, generalized rash, bullous skin reactions), and eye inflammation (iritis, uveitis) have been reported rarely (6.2)
To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-521-8813 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of Atelvia (7.1)

USE IN SPECIFIC POPULATIONS

Atelvia is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) (5.6, 8.6, 12.3)
Atelvia is not indicated for use in pediatric patients (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 05/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Postmenopausal Osteoporosis

Atelvia is indicated for the treatment of osteoporosis in postmenopausal women. Bone mineral density increases achieved at one year with Atelvia are non-inferior to increases seen with risedronate sodium 5 mg (immediate-release) daily. Daily risedronate sodium 5 mg (immediate-release) has been shown to reduce the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures [see *Clinical Studies (14.1)*].

1.2 Important Limitations of Use

The safety and effectiveness of Atelvia for the treatment of osteoporosis are based on clinical data of one year duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

2 DOSAGE AND ADMINISTRATION

Atelvia should be taken in the morning immediately following breakfast.

When compared with immediate-release risedronate, treatment with Atelvia resulted in a significantly higher incidence of abdominal pain when administered before breakfast under fasting conditions. Atelvia should be taken immediately following breakfast and not under fasting conditions.

To facilitate delivery to the stomach, Atelvia should be swallowed whole while the patient is in an upright position and with at least 4 ounces of plain water. Tablets should not be chewed, cut, or crushed. Patients should not lie down for 30 minutes after taking the medication [see *Warnings and Precautions (5.2)*].

Patients should receive supplemental calcium and vitamin D [see *Warnings and Precautions (5.3)*)]. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of Atelvia and it is recommended they be taken at a different time of the day. Atelvia is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min or in the elderly.

2.1 Treatment of Postmenopausal Osteoporosis

[see *Indications and Usage (1.1)*]

The recommended regimen is:

- one 35 mg delayed-release tablet orally, taken once-a-week

3 DOSAGE FORMS AND STRENGTHS

Delayed-release tablets: 35 mg, yellow, oval-shaped, and engraved with EC 35 on one side.

4 CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia [see *Warnings and Precautions (5.2)*]
- Inability to stand or sit upright for at least 30 minutes [see *Dosage and Administration (2), Warnings and Precautions (5.2)*]
- Hypocalcemia [see *Warnings and Precautions (5.3)*]
- Known hypersensitivity to any component of this product [see *Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with the Same Active Ingredient

Atelvia contains the same active ingredient found in Actonel®. A patient being treated with Actonel should not receive Atelvia.

5.2 Upper Gastrointestinal Adverse Reactions

Atelvia, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Atelvia is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers) [see *Contraindications (4), Adverse Reactions (6.1), Information for Patients (17)*].

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. In some cases, these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms

signaling a possible esophageal reaction and patients should be instructed to discontinue Atelvia and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.
The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates and/or who fail to swallow it with the recommended 4 oz. of water, and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient [see *Dosage and Administration (2)*]. In patients who cannot comply with dosing instructions due to mental disability, therapy with Atelvia should be used under appropriate supervision.
There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

5.3 Mineral Metabolism
Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Atelvia therapy. Adequate intake of calcium and vitamin D is important in all patients [see *Contraindications (4), Adverse Reactions (6.1), Information for Patients (17)*].

5.4 Jaw Osteonecrosis
Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including risedronate. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).
For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.
Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment [see *Adverse Reactions (6.2)*]

5.5 Musculoskeletal Pain
In postmarketing experience, there have been reports of severe and occasionally incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates [see *Adverse Reactions (6.2)*]. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

5.6 Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are traverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.
Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.7 Renal Impairment
Atelvia is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience.

5.8 Laboratory Test Interactions
Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with Atelvia have not been performed.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Treatment of Postmenopausal Osteoporosis

Once-a-Week Dosing with Atelvia (risedronate sodium) delayed-release tablets

The safety of Atelvia 35 mg once-a-week in the treatment of postmenopausal osteoporosis was assessed in a 1-year, double-blind, multicenter study comparing Atelvia 35 mg once-a-week to risedronate sodium immediate-release 5 mg daily in postmenopausal women 50 years of age or older. Atelvia was administered either at least 30 minutes before (N = 308) or immediately following (N = 307) breakfast, and risedronate sodium immediate-release 5 mg daily (N = 307) was administered at least 30 minutes before breakfast. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H_2 antagonists were included in this clinical trial. All women received daily supplementation with 1000 mg of elemental calcium plus 800 to 1000 IU vitamin D. As treatment with Atelvia resulted in a significantly higher incidence of abdominal pain when administered before breakfast under fasting conditions, safety results that follow refer only to Atelvia 35 mg once-a-week immediately following breakfast and risedronate sodium immediate-release 5 mg daily.

The incidence of all-cause mortality was 0.0% in the Atelvia 35 mg once-a-week group and 0.3% in the risedronate sodium immediate-release 5 mg daily group. The incidence of serious adverse reactions was 6.5% in the Atelvia 35 mg once-a-week group and 7.2% in the risedronate sodium immediate-release 5 mg daily group. The percentage of patients who withdrew from the study due to adverse reactions was 9.1% in the Atelvia 35 mg once-a-week group and 8.1% in the risedronate sodium immediate-release 5 mg daily group. The overall safety and tolerability profiles of the two dosing regimens were similar. Table 1 lists adverse reactions reported in ≥2% of patients. Adverse reactions are shown without attribution of causality.

Table 1. Adverse Reactions Occurring at a Frequency of ≥2% in Either Treatment Group

	35 mg Atelvia	**5 mg Risedronate sodium Immediate- release**
	Weekly	**Daily**
System Organ Class	**N = 307**	**N = 307**
Preferred Term	**%**	**%**
Gastrointestinal disorders		
Diarrhea	8.8	4.9
Abdominal pain	5.2	2.9
Constipation	4.9	2.9
Vomiting	4.9	1.6
Dyspepsia	3.9	3.9
Nausea	3.6	3.9
Abdominal pain upper	2.9	2.3
Infections and infestations		
Influenza	7.2	6.2
Bronchitis	3.9	4.2
Upper respiratory tract infection	3.6	2.6
Musculoskeletal and connective tissue disorders		
Arthralgia	6.8	7.8
Back pain	6.8	5.9
Pain in extremity	3.9	2.3
Musculoskeletal pain	2.0	1.6
Muscle spasms	1.0	2.3
Nervous system disorders		
Dizziness	2.6	3.3
Headache	2.6	4.9

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of acute phase reaction was 2.3% in the Atelvia 35 mg once-a-week group and 1.3% in the risedronate sodium immediate-release 5 mg daily group. These incidence rates are based on reporting of one or more pre-specified acute phase reaction-like symptoms within 3 days of the first dose and for a duration of 7 days or less.

Gastrointestinal Adverse Reactions: Adverse reactions related to the upper gastrointestinal tract occurred in 16% of subjects treated with Atelvia 35 mg once-a-week and 15% of subjects treated with risedronate sodium immediate-release 5 mg daily. The incidence of upper gastrointestinal tract adverse reactions in the Atelvia 35 mg once-a-week and risedronate sodium immediate-release 5 mg daily groups were: abdominal pain (5.2% versus 2.9%), dyspepsia (3.9% versus 3.9%), upper abdominal pain (2.9% versus 2.3%), gastritis

(1.0% versus 1.0%), and gastroesophageal reflux disease (1.0% versus 1.6%). Study discontinuation due to abdominal pain occurred in 1.3% of the Atelvia 35 mg once-a-week group and 0.7% of the risedronate sodium immediate-release 5 mg daily group.
Musculoskeletal Adverse Reactions: Selected musculoskeletal adverse reactions were reported in 16% of subjects treated with Atelvia 35 mg once-a-week and 15% of subjects treated with risedronate sodium immediate-release 5 mg daily. The incidence of musculoskeletal adverse reactions in the Atelvia 35 mg once-a-week and risedronate sodium immediate-release 5 mg daily groups were: arthralgia (6.8% versus 7.8%), back pain (6.8% versus 5.9%), musculoskeletal pain (2.0% versus 1.6%), and myalgia (1.3% versus 1.0%).
Laboratory Test Findings:
Parathyroid hormone: The effect of Atelvia 35 mg once-a-week and risedronate sodium immediate-release 5 mg daily on parathyroid hormone was evaluated in postmenopausal women with osteoporosis. At week 52, in subjects with normal levels at baseline, PTH levels greater than 65 pg/mL (upper limit of normal) were noted in 9% of subjects receiving Atelvia 35 mg once-a-week and 8% of subjects receiving risedronate sodium immediate-release 5 mg daily. In subjects with normal levels at baseline, PTH levels greater than 97 pg/mL (1.5 times the upper limit of normal) were seen in 2% of subjects receiving Atelvia 35 mg once-a-week and no subjects receiving risedronate sodium immediate-release 5 mg daily. There were no clinically significant differences between treatment groups for levels of calcium, phosphorus and magnesium.
Daily Dosing with risedronate sodium immediate-release 5 mg tablets
The safety of risedronate sodium immediate-release 5 mg once daily in the treatment of postmenopausal osteoporosis was assessed in four randomized, double-blind, placebo-controlled multinational trials of 3232 women aged 38 to 85 years with postmenopausal osteoporosis. The duration of the trials was up to three years, with 1619 patients exposed to placebo and 1613 patients exposed to risedronate sodium immediate-release 5 mg daily. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors (PPIs), and H_2 antagonists were included in these clinical trials. All women received 1000 mg of elemental calcium plus vitamin D supplementation up to 500 IU per day if their 25-hydroxyvitamin D_3 level was below normal at baseline.
The incidence of all-cause mortality was 2.0% in the placebo group and 1.7% in the risedronate sodium immediate-release 5 mg daily group. The incidence of serious adverse reactions was 24.6% in the placebo group and 27.2% in the risedronate sodium immediate-release 5 mg daily group. The percentage of patients who withdrew from the study due to adverse reactions was 15.6% in the placebo group and 14.8% in the risedronate sodium immediate-release 5 mg daily group. The most common adverse reactions reported in >10% of subjects were: back pain, arthralgia, abdominal pain and dyspepsia.
Gastrointestinal Adverse Reactions: The incidence of adverse reactions in the placebo and risedronate sodium immediate-release 5 mg daily groups were: abdominal pain (9.9% versus 12.2%), diarrhea (10.0% versus 10.8%), dyspepsia (10.6% versus 10.8%), and gastritis (2.3% versus 2.7%). Duodenitis and glossitis have been reported uncommonly in the risedronate sodium immediate-release 5 mg daily group (0.1% to 1%). In patients with active upper gastrointestinal disease at baseline, the incidence of upper gastrointestinal adverse reactions was similar between the placebo and risedronate sodium immediate-release 5 mg daily groups.
Musculoskeletal Adverse Reactions: The incidence of adverse reactions in the placebo and risedronate sodium immediate-release 5 mg daily groups were: back pain (26.1% versus 28.0%), arthralgia (22.1% versus 23.7%), myalgia (6.2% versus 6.7%), and bone pain (4.8% versus 5.3%).
Laboratory Test Findings: Throughout the Phase 3 studies, transient decreases from baseline in serum calcium (<1%) and serum phosphate (<3%) and compensatory increases in serum PTH levels (<30%) were observed within 6 months in patients in osteoporosis clinical trials treated with risedronate sodium immediate-release 5 mg daily. There were no significant differences in serum calcium, phosphate, or PTH levels between placebo and risedronate sodium immediate- release 5 mg daily at 3 years. Serum calcium levels below 8 mg/dL were observed in 18 patients, 9 (0.5%) in each treatment arm (placebo and risedronate sodium immediate-release 5 mg daily). Serum phosphorus levels below 2 mg/dL were observed in 14 patients, 3 (0.2%) treated with placebo and 11 (0.6%) treated with risedronate sodium immediate-release 5 mg daily. There have been rare reports (<0.1%) of abnormal liver function tests.
Endoscopic Findings: In the risedronate sodium immediate-release 5 mg daily clinical trials, endoscopic evaluation was encouraged in any patient with moderate-to-severe gastrointestinal complaints, while maintaining the blind. Endoscopies were performed on equal numbers of patients between the placebo and treated groups [75 (14.5%) placebo; 75 (11.9%) risedronate sodium immediate-release 5 mg daily]. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (51% placebo; 39% risedronate sodium immediate-release 5 mg daily).

6.2 Postmarketing Experience
Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
The following adverse reactions have been reported with the use of risedronate sodium immediate-release.
Hypersensitivity Reactions
Hypersensitivity and skin reactions have been reported rarely, including angioedema, generalized rash and bullous skin reactions, some severe.
Gastrointestinal Adverse Reactions
Reactions involving upper gastrointestinal irritation, such as esophagitis and esophageal or gastric ulcers, have been reported [see *Warnings and Precautions (5.2)*].

Musculoskeletal Pain
Bone, joint, or muscle pain, described as severe or incapacitating, have been reported rarely [see *Warnings and Precautions (5.5)*].
Eye Inflammation
Reactions of eye inflammation including iritis and uveitis have been reported rarely.
Jaw Osteonecrosis
Osteonecrosis of the jaw has been reported rarely [see *Warnings and Precautions (5.4)*].

7 DRUG INTERACTIONS

Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (e.g., Cytochrome P450).

7.1 Calcium Supplements/Antacids

When Atelvia was administered following breakfast, the co-administration of a tablet containing 600 mg of elemental calcium and 400 IU vitamin D reduced risedronate bioavailability by approximately 38% [see *Clinical Pharmacology (12.3)*]. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations may reduce the bioavailability of Atelvia and should not be taken together.

7.2 Hormone Therapy

Concomitant use of Atelvia with estrogens and estrogen agonist/antagonists has not been studied.

7.3 Aspirin/Nonsteroidal Anti-Inflammatory Drugs

In the Phase 3 study comparing Atelvia 35 mg once-a-week immediately following breakfast and risedronate sodium 5 mg daily, 18% of NSAID users (any use) in both groups developed upper gastrointestinal adverse reactions. Among non-users, 13% of patients taking Atelvia 35 mg once-a-week immediately following breakfast developed upper gastrointestinal adverse reactions, compared to 12% taking risedronate sodium 5 mg daily.

7.4 Histamine 2 (H_2) Blockers, Proton Pump Inhibitors (PPIs), and Antacids

Drugs that raise stomach pH (e.g., H_2 blockers, PPIs, or antacids) may affect the enteric coating on Atelvia tablets and thereby reduce bioavailability of Atelvia. The effects of concomitant administration of H_2 blockers, PPIs, and antacids on bioavailability of Atelvia have not been been evaluated.
Atelvia should not be taken at the same time with antacids. Concomitant administration of Atelvia and H_2 blockers or PPIs is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies of Atelvia in pregnant women. Atelvia should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.
Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over periods of weeks to years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been studied.
In animal studies, pregnant rats received risedronate sodium during organogenesis at doses 1 to 26 times the human Paget's disease dose of 30 mg/day. Survival of neonates was decreased in rats treated during gestation with oral doses approximately 5 times the human dose and body weight was decreased in neonates from dams treated with approximately 26 times the human dose. The number of fetuses exhibiting incomplete ossification of sternebrae or skull from dams treated with approximately 2.5 times the human dose was significantly increased compared to controls. Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses approximately 5 times the human dose. A low incidence of cleft palate was observed in fetuses from female rats treated with oral doses approximately equal to the human dose. The relevance of this finding to human use of Atelvia is unclear.
No significant fetal ossification effects were seen in rabbits treated with oral doses approximately 7 times the human dose (the highest dose tested). However, 1 of 14 litters were aborted and 1 of 14 litters were delivered prematurely.
Similar to other bisphosphonates, treatment during mating and gestation with doses of risedronate sodium approximately the same as the human Paget's disease dose of 30 mg/day resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver. Dosing multiples provided above are based on the recommended human Paget's disease dose of 30 mg/day and normalized using body surface area (mg/m^2). Actual animal doses were 3.2, 7.1 and 16 mg/kg/day in the rat and 10 mg/kg/day in the rabbit.

8.3 Nursing Mothers

Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period post-dosing, indicating a small degree of lacteal transfer. It is not known whether Atelvia is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Atelvia, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Atelvia is not indicated for use in pediatric patients.

The safety and effectiveness of risedronate sodium immediate-release was assessed in a one-year, randomized, double-blind, placebo-controlled study of 143 pediatric patients (94 received risedronate) with osteogenesis imperfecta (OI). The enrolled population was predominantly patients with mild OI (85% Type-I), aged 4 to <16 years, 50% male and 82% Caucasian, with a mean lumbar spine BMD Z-score of -2.08 (2.08 standard deviations below the mean for age-matched controls). Patients received either a 2.5 mg (≤30 kg body weight) or 5 mg (>30 kg body weight) daily oral dose. After one year, an increase in lumbar spine BMD in the risedronate sodium immediate-release group compared to the placebo group was observed. However, treatment with risedronate sodium immediate-release did not result in a reduction in the risk of fracture in pediatric patients with OI. In risedronate sodium immediate-release treated subjects, no mineralization defects were noted in paired bone biopsy specimens obtained at baseline and month 12.

The overall safety profile of risedronate in OI patients treated for up to 12 months was generally similar to that of adults with osteoporosis. However, there was an increased incidence of vomiting compared to placebo. In this study, vomiting was observed in 15% of children treated with risedronate sodium immediate-release and 6% of patients treated with placebo. Other adverse reactions reported in ≥10% of patients treated with risedronate sodium immediate-release and with a higher frequency than placebo were: pain in the extremity (21% with risedronate sodium immediate-release versus 16% with placebo), headache (20% versus 8%), back pain (17% versus 10%), pain (15% versus 10%), upper abdominal pain (11% versus 8%), and bone pain (10% versus 4%).

8.5 Geriatric Use

Of the patients receiving Atelvia in postmenopausal osteoporosis studies, 59% were 65 and over, while 13% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Atelvia is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min.

8.7 Hepatic Impairment

No studies have been performed to assess risedronate sodium's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in human liver preparations. Dosage adjustment is unlikely to be needed in patients with hepatic impairment.

10 OVERDOSAGE

Decreases in serum calcium and phosphorus following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients. While milk or antacids containing calcium may be given to bind risedronate sodium immediate-release and reduce absorption of the drug, the impact of this intervention for Atelvia delayed-release tablets has not been evaluated.

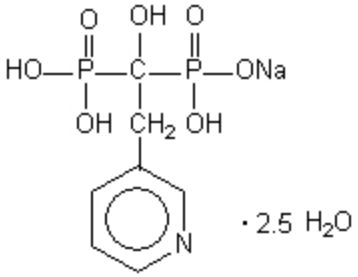
In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug. Standard procedures that are effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

Lethality after single oral doses of risedronate was seen in female rats at 903 mg/kg and male rats at 1703 mg/kg. The minimum lethal dose in mice and rabbits was 4000 mg/kg and 1000 mg/kg, respectively. These values represent 320 to 620 times the human Paget's disease dose of 30 mg/day based on surface area (mg/m^2).

11 DESCRIPTION

Atelvia (risedronate sodium) delayed-release tablets contain a pH-sensitive enteric coating and a chelating agent (EDTA). Risedronate is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism.

Each Atelvia tablet for oral administration contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. The empirical formula for risedronate sodium hemi-pentahydrate is $C_7H_{10}NO_7P_2Na \cdot 2.5\ H_2O$. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt. The chemical structure of risedronate sodium hemi-pentahydrate is the following:



Molecular Weight:
Anhydrous: 305.10
Hemi-pentahydrate: 350.13
Risedronate sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions, and essentially insoluble in common organic solvents.
Inactive Ingredients
Edetate disodium, ferric oxide yellow, magnesium stearate, methacrylic acid copolymer, polysorbate 80, silicified microcrystalline cellulose (ProSolv SMCC90), simethicone, sodium starch glycolate, stearic acid, talc, and triethyl citrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Risedronate has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, risedronate inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (e.g., lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that risedronate treatment reduces bone turnover (activation frequency, i.e., the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

12.2 Pharmacodynamics
Risedronate treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of risedronate sodium immediate-release to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone-specific alkaline phosphatase (a marker of bone formation). At the 5 mg daily dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone-specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years. Bone turnover is decreased as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1-year study comparing Atelvia 35 mg weekly taken immediately after breakfast versus risedronate sodium immediate-release 5 mg daily oral dosing regimens in postmenopausal women, mean decreases from baseline at 1 year in urinary collagen cross-linked N-telopeptide were 47% in the Atelvia 35 mg once-a-week following breakfast group and 42% in the risedronate sodium immediate-release 5 mg daily group.
In addition, serum bone-specific alkaline phosphatase at 1 year was reduced by 33% in the Atelvia 35 mg once-a-week following breakfast group and 32% in the risedronate sodium immediate-release 5 mg daily group.

12.3 Pharmacokinetics
Absorption
The mean absolute oral bioavailability of the 30 mg risedronate sodium immediate-release tablet taken 4 hours prior to a meal is 0.63% (90% confidence interval [CI]: 0.54% to 0.75%) and is similar to an oral solution. The time to peak concentration (T_{max}) for Atelvia tablet is ~3 hours when administered in the morning 4 hours prior to a meal.
Food Effect
In a crossover pharmacokinetic study, the bioavailability of Atelvia 35 mg delayed-release tablets decreased by ~30% when administered immediately after a high-fat breakfast compared to administration in the morning 4 hours before a meal.
The bioavailability of the 35 mg Atelvia tablet administered after a high-fat breakfast was similar to risedronate sodium 35 mg immediate-release tablet dosed 4 hours before a meal in one study and was approximately 2- to 4-fold greater than the immediate-release 35 mg tablet administered 30 minutes prior to a high-fat breakfast.
In a separate study, Atelvia administered after dinner exhibited approximately 87% increase in risedronate exposure compared to administration following a breakfast. The safety and efficacy of dosing Atelvia after dinner has not been evaluated [see *Dosage and Administration (2)*].
Distribution

The mean steady-state volume of distribution for risedronate is 13.8 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was in the range of 0.001% to 0.01%.

Metabolism

There is no evidence of systemic metabolism of risedronate.

Excretion

In young healthy subjects, approximately half of the absorbed dose of risedronate was excreted in urine within 24 hours, and 85% of an intravenous dose was recovered in the urine over 28 days. Based on simultaneous modeling of serum and urine data for the risedronate sodium immediate-release tablets, mean renal clearance was 105 mL/min (CV = 34%) and mean total clearance was 122 mL/min (CV = 19%), with the difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. In osteopenic postmenopausal women, the terminal exponential half-life was 561 hours, mean renal clearance was 52 mL/min (CV = 25%), and mean total clearance was 73 mL/min (CV = 15%).

Specific Populations

Pediatric: Atelvia is not indicated for use in pediatric patients [see *Pediatric Use (8.4)*].

Geriatric: Effect of age on bioavailability of Atelvia has not been evaluated. Based on data from risedronate immediate-release tablet, bioavailability and disposition of risedronate are similar in elderly (>60 years of age) and younger subjects. No dosage adjustment is necessary.

Race: Pharmacokinetic differences due to race have not been studied. The clinical trial of Atelvia was conducted mostly in Caucasians.

Renal Impairment: Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 mL/min. Atelvia is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min.

Hepatic Impairment: No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (<0.1% of intravenous dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

Drug Interactions: Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (e.g., Cytochrome P450).

Calcium supplement: A Phase 1 single-dose, cross-over study in 101 postmenopausal women evaluated the relative bioavailability of Atelvia 35 mg delayed-release tablets taken after breakfast and following a 600 mg elemental calcium/400 IU vitamin D supplement, compared to Atelvia alone taken after breakfast without calcium or vitamin D supplemention. The addition of the calcium/vitamin D supplement following the meal resulted in an approximate 38% reduction in the amount of risedronate absorbed [see *Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week carcinogenicity study, rats were administered daily oral doses up to approximately 8 times the human Paget's disease dose of 30 mg/day. There were no significant drug-induced tumor findings in male or female rats. The high dose male group was terminated early in the study (Week 93) due to excessive toxicity, and data from this group were not included in the statistical evaluation of the study results. In an 80-week carcinogenicity study, mice were administered daily oral doses approximately 6.5 times the human dose. There were no significant drug-induced tumor findings in male or female mice.

Mutagenesis

Risedronate did not exhibit genetic toxicity in the following assays: *In vitro* bacterial mutagenesis in *Salmonella* and *E. coli* (Ames assay), mammalian cell mutagenesis in CHO/HGPRT assay, unscheduled DNA synthesis in rat hepatocytes and an assessment of chromosomal aberrations *in vivo* in rat bone marrow. Risedronate was positive in a chromosomal aberration assay in CHO cells at highly cytotoxic concentrations (>675 mcg/mL, survival of 6% to 7%). When the assay was repeated at doses exhibiting appropriate cell survival (29%), there was no evidence of chromosomal damage.

Impairment of Fertility

In female rats, ovulation was inhibited at an oral dose approximately 5 times the human dose. Decreased implantation was noted in female rats treated with doses approximately 2.5 times the human dose. In male rats, testicular and epididymal atrophy and inflammation were noted at approximately 13 times the human dose. Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses approximately 5 times the human dose. There was moderate-to-severe spermatid maturation block after 13 weeks in male dogs at an oral dose approximately 8 times the human dose. These findings tended to increase in severity with increased dose and exposure time.

Dosing multiples provided above are based on the recommended human Paget's disease dose of 30 mg/day and normalized using body surface area (mg/m^2). Actual doses were 24 mg/kg/day in rats, 32 mg/kg/day in mice, and 8, 16 and 40 mg/kg/day in dogs.

13.2 Animal Toxicology and/or Pharmacology

Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized rats and minipigs. Bone mass and biomechanical strength were increased dose-dependently at daily oral doses up to 4 and 25 times the recommended human dose of 5 mg/day for rats and minipigs, respectively. Risedronate treatment maintained the positive correlation between BMD and bone strength and did not have a negative effect on bone structure or mineralization. In intact dogs, risedronate induced positive bone balance at the level of the bone remodeling unit at oral doses ranging from 0.5 to 1.5 times the human dose of 5 mg/day.

In dogs treated with an oral dose approximately 5 times the human dose of 5 mg/day, risedronate caused a delay in fracture healing of the radius. The observed delay in fracture healing is similar to other bisphosphonates. This effect did not occur at a dose approximately 0.5 times the human daily dose.

The Schenk rat assay, based on histologic examination of the epiphyses of growing rats after drug treatment, demonstrated that risedronate did not interfere with bone mineralization even at the highest dose tested, which was approximately 3500 times the lowest antiresorptive dose in this model (1.5 mcg/kg/day) and approximately 800 times the human dose of 5 mg/day. This indicates that Atelvia administered at the therapeutic dose is unlikely to induce osteomalacia.

Dosing multiples provided above are based on the recommended human osteoporosis dose of 5 mg/day and normalized using body surface area (mg/m^2).

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

The efficacy of Atelvia 35 mg once-a-week in the treatment of postmenopausal osteoporosis was demonstrated in a randomized, double-blind, active-control trial of approximately 900 subjects. All patients in this study received supplemental calcium (1000 mg/day) and vitamin D (800 to 1000 IU/day). The primary efficacy endpoint was percent change in lumbar spine bone mineral density at 1 year.

Atelvia 35 mg once-a-week administered after breakfast was shown to be non-inferior to risedronate sodium immediate-release 5 mg daily. Table 2 presents the primary efficacy analysis, percent change in lumbar spine BMD, in the intent-to-treat population with last observation carried forward (LOCF).

Table 2. Lumbar Spine BMD - Percent Change from Baseline at Endpoint*

	Risedronate sodium immediate-release 5 mg Daily N = 307	Atelvia 35 mg Once-a-Week Following Breakfast N = 307
Primary Efficacy (LOCF)		
n	270	261
LS Mean (95% CI)	3.1† (2.7, 3.5)	3.3† (2.9, 3.7)
LS Mean Difference‡ (95% CI)		-0.2 (-0.8, 0.3)

N = number of intent-to-treat patients within specified treatment; n = number of patients with values at the visit.
LS = Least Squares

*at 1 year LOCF
†Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons.
‡LS Mean Difference is 5 mg daily minus 35 mg weekly treatment.

Fracture efficacy with risedronate sodium immediate-release 5 mg daily

The fracture efficacy of risedronate sodium immediate-release 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in 2 large, randomized, placebo-controlled, double-blind studies that enrolled a total of almost 4000 postmenopausal women under similar protocols. The Multinational study (VERT MN) (risedronate sodium immediate-release 5 mg daily, N = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (VERT NA) (risedronate sodium immediate-release 5 mg daily, N = 821). Patients were selected on the basis of radiographic evidence of previous vertebral fracture, and therefore, had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in VERT MN, and 2.5 in VERT NA, with a broad range of baseline BMD levels. All patients in these studies received supplemental calcium 1000 mg/day. Patients with low 25-hydroxyvitamin D_3 levels (approximately 40 nmol/L or less) also received 500 IU/day supplemental vitamin D.

Effect on Vertebral Fractures

Fractures of previously undeformed vertebrae (new fractures) and worsening of pre-existing vertebral fractures were diagnosed radiographically; some of these fractures were also associated with symptoms (i.e., clinical fractures). Spinal radiographs were scheduled annually and prospectively planned analyses were based on the time to a patient's first diagnosed fracture. The primary endpoint for these studies was the incidence of new and worsening vertebral fractures across the period of 0 to 3 years. Risedronate sodium immediate-release 5 mg daily significantly reduced the incidence of new and worsening vertebral fractures and of new vertebral fractures in both VERT NA and VERT MN at all time points (Table 3). The reduction in risk seen in the subgroup of patients who had 2 or more vertebral fractures at study entry was similar to that seen in the overall study population.

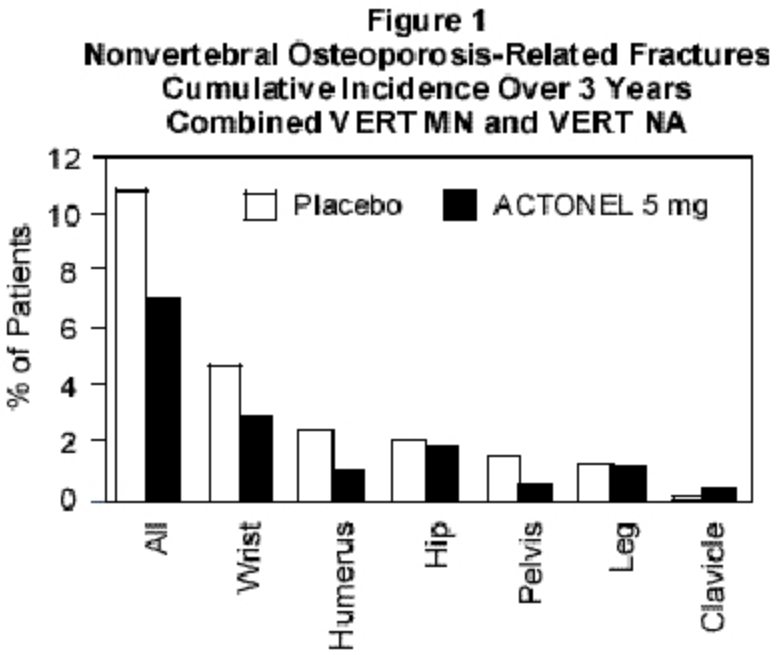
Table 3. The Effect of Risedronate sodium 5 mg Immediate-Release Daily on the Risk of Vertebral Fractures

	Proportion of Patients with Fracture (%)*			
VERT NA	Placebo N = 678	Risedronate sodium 5 mg N = 696	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 to 1 Year	7.2	3.9	3.3	49
0 to 2 Years	12.8	8.0	4.8	42
0 to 3 Years	18.5	13.9	4.6	33
New				
0 to 1 Year	6.4	2.4	4.0	65
0 to 2 Years	11.7	5.8	5.9	55
0 to 3 Years	16.3	11.3	5.0	41
VERT MN	Placebo N = 346	Risedronate sodium 5 mg N = 344	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 to 1 Year	15.3	8.2	7.1	50
0 to 2 Years	28.3	13.9	14.4	56
0 to 3 Years	34.0	21.8	12.2	46
New				
0 to 1 Year	13.3	5.6	7.7	61
0 to 2 Years	24.7	11.6	13.1	59
0 to 3 Years	29.0	18.1	10.9	49

*****Calculated by Kaplan-Meier methodology.

Effect on Osteoporosis-Related Nonvertebral Fractures

In VERT MN and VERT NA, a prospectively planned efficacy endpoint was defined consisting of all radiographically confirmed fractures of skeletal sites accepted as associated with osteoporosis. Fractures at these sites were collectively referred to as osteoporosis-related nonvertebral fractures. Risedronate sodium immediate-release 5 mg daily significantly reduced the incidence of nonvertebral osteoporosis-related fractures over 3 years in VERT NA (8% versus 5%; relative risk reduction 39%) and reduced the fracture incidence in VERT MN from 16% to 11%. There was a significant reduction from 11% to 7% when the studies were combined, with a corresponding 36% reduction in relative risk. Figure 1 shows the overall results as well as the results at the individual skeletal sites for the combined studies.



Histology/Histomorphometry

Bone biopsies from 110 postmenopausal women were obtained at endpoint in the VERT NA study. Patients had received placebo or daily risedronate sodium immediate-release (2.5 mg or 5 mg) for 2 to 3 years. Histologic evaluation (N = 103) showed no osteomalacia, impaired bone mineralization, or other adverse effects on bone in risedronate sodium immediate-release treated women. These findings demonstrate that bone formed during risedronate sodium immediate- release administration is of normal quality.

The histomorphometric parameter mineralizing surface, an index of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 21 treated with placebo and 23 patients treated with risedronate sodium immediate- release 5 mg daily. Mineralizing surface decreased moderately in risedronate sodium immediate- release treated patients (median percent change: placebo, -21%; risedronate sodium immediate- release 5 mg daily, -74%), consistent with the known effects of treatment on bone turnover.

Effect on Height

In the two 3-year osteoporosis treatment studies, standing height was measured yearly by stadiometer. Both risedronate sodium immediate-release 5 mg daily and placebo-treated groups lost height during the studies. Patients who received risedronate sodium immediate-release 5 mg daily had a statistically significantly smaller loss of height than those who received placebo. In VERT MN, the median annual height change was -2.4 mm/yr in the placebo group compared to -1.3 mm/yr in the risedronate sodium immediate-release 5 mg daily group. In VERT NA, the median annual height change was -1.1 mm/yr in the placebo group compared to -0.7 mm/yr in the risedronate sodium immediate-release 5 mg daily group.

Effect on Bone Mineral Density

The results of 4 randomized, placebo-controlled trials in women with postmenopausal osteoporosis (VERT MN, VERT NA, BMD MN, BMD NA) demonstrate that risedronate sodium immediate-release 5 mg daily increases BMD at the spine, hip, and wrist compared to the effects seen with placebo. Table 4 displays the significant increases in BMD seen at the lumbar spine, femoral neck, femoral trochanter, and midshaft radius in these trials compared to placebo. In both VERT studies (VERT MN and VERT NA), risedronate sodium immediate-release 5 mg daily produced increases in lumbar spine BMD that were progressive over the 3 years of treatment, and were statistically significant relative to baseline and to placebo at 6 months and at all later time points.

Table 4. Mean Percent Increase in BMD from Baseline in Patients Taking Risedronate sodium Immediate-Release 5 mg or Placebo at Endpoint*

	VERT MN†		VERT NA†		BMD MN‡		BMD NA‡	
	Placebo N = 323	5 mg N = 323	Placebo N = 599	5 mg N = 606	Placebo N = 161	5 mg N = 148	Placebo N = 191	5 mg N = 193
Lumbar Spine	1.0	6.6	0.8	5.0	0.0	4.0	0.2	4.8
Femoral Neck	-1.4	1.6	-1.0	1.4	-1.1	1.3	0.1	2.4
Femoral Trochanter	-1.9	3.9	-0.5	3.0	-0.6	2.5	1.3	4.0
Midshaft Radius	-1.5§	0.2§	-1.2§	0.1§	ND		ND	
ND = analysis not done								

*The endpoint value is the value at the study's last time point for all patients who had BMD measured at that time; otherwise the last post-baseline BMD value prior to the study's last time point is used.
†The duration of the studies was 3 years.
‡The duration of the studies was 1.5 to 2 years.
§BMD of the midshaft radius was measured in a subset of centers in VERT MN (placebo, N = 222; 5 mg, N = 214) and VERT NA (placebo, N = 310; 5 mg, N = 306).

16 HOW SUPPLIED/STORAGE AND HANDLING

Atelvia™ (risedronate sodium) delayed-release tablets are:
35 mg, yellow, oval-shaped, and engraved with EC 35 on one side.
NDC 0430-0979-03 Dosepak of 4 tablets
Store at controlled room temperature 20° to 25° C (68° to 77° F) [*see* USP].

17 PATIENT COUNSELING INFORMATION

[*See FDA-Approved Patient Labeling*]
The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions.
Patients should not take Atelvia if they have abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia, inability to stand or sit upright for at least 30 minutes, hypocalcemia, or known hypersensitivity to any component of this product [see *Contraindications (4)*].
Atelvia and Actonel contain the same active ingredient. Patients receiving Actonel should not receive Atelvia [see *Warnings and Precautions (5.1)*]
To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, patients should take Atelvia in the morning, while in an upright position (sitting or standing) with at least 4 ounces of plain water immediately following breakfast. Atelvia should not be taken before breakfast. Patients must swallow Atelvia tablets whole. Patients should not chew, cut, or crush the tablet because of a potential for oropharyngeal irritation, and because the tablet coating is an important part of the delayed-release formulation. Patients should not lie down for 30 minutes after taking the medication
Severe irritation of the upper gastrointestinal (GI) mucosa can occur. Caution should be used in patients with active upper GI disease. Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or severe persistent or worsening heartburn) they should consult their physician before continuing Atelvia [see *Warnings and Precautions (5.2)*]
Patients should receive supplemental calcium and vitamin D. Hypocalcemia may worsen and must be corrected prior to use [see *Warnings and Precautions (5.3)*]. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of Atelvia and should be taken at a different time of the day.
Osteonecrosis of the jaw has been reported rarely [see *Warnings and Precautions (5.4)*]. Severe bone, joint, or muscle pain may occur. Consider discontinuing use if severe symptoms develop [see *Warnings and Precautions (5.5)*]. Atelvia is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience [see *Warnings and Precautions (5.6)*].
Most common adverse reactions while taking Atelvia include diarrhea, influenza, arthralgia, back pain, and abdominal pain [see *Adverse Reactions (6.1)*]. Hypersensitivity reactions (angioedema, generalized rash, bullous skin reactions), and eye inflammation (iritis, uveitis) have been reported rarely [see *Adverse Reactions (6.2)*].
Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as excessive cigarette smoking, and/or alcohol consumption, if these factors exist.
Patients should be instructed that if they miss a dose of Atelvia 35 mg once-a-week, they should take 1 tablet on the morning after they remember and return to taking 1 tablet once-a-week, as originally scheduled on their chosen day. Patients should not take 2 tablets on the same day.
Physicians should instruct their patients to read the Medication Guide before starting therapy with Atelvia and to re-read it each time the prescription is renewed.
Patients should be reminded to give all of their healthcare providers an accurate medication history. Instruct patients to tell all of their healthcare providers that they are taking Atelvia. Patients should be instructed that any time they have a medical problem they think may be from Atelvia they should talk to their doctor.

MEDICATION GUIDE

Medication Guide
Atelvia™ (uh-TEL-v-uh)
(risedronate sodium)
delayed-release tablets

Read this Medication Guide that comes with Atelvia™ before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. Talk to your doctor if you have any questions about Atelvia.

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

Atelvia can cause serious side effects including:

1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Severe jaw bone problems (osteonecrosis)
4. Bone, joint, or muscle pain
5. Unusual thigh bone fractures

1. Esophagus problems.

Some people who take Atelvia may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

- **It is important that you take Atelvia exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take Atelvia?")**
- **Stop taking Atelvia and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.**

2. Low calcium levels in your blood (hypocalcemia).

Atelvia may lower the calcium levels in your blood. If you have low blood calcium before you start taking Atelvia, it may get worse during treatment. Your low blood calcium must be treated before you take Atelvia. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you are taking Atelvia. Take calcium and vitamin D as your doctor tells you to.

3. Severe jaw bone problems (osteonecrosis).

Severe jaw bone problems may happen when you take Atelvia. Your doctor should examine your mouth before you start Atelvia. Your doctor may tell you to see your dentist before you start Atelvia. It is important for you to practice good mouth care during treatment with Atelvia.

4. Bone, joint, or muscle pain.

Some people who take Atelvia develop severe bone, joint, or muscle pain.

5. Unusual thigh bone fractures.

Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is Atelvia?

Atelvia is a prescription medicine used to treat osteoporosis in women after menopause.

It is not known how long Atelvia works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if Atelvia is still right for you.

Atelvia is not for use in children.

Who should not take Atelvia?

Do not take Atelvia if you:

- Have certain problems with your esophagus, the tube that connects your mouth and stomach
- Cannot sit or stand up for at least 30 minutes
- Have low blood calcium (hypocalcemia)
- Are allergic to any of the other ingredients in Atelvia. See the end of this leaflet for a complete list of ingredients in Atelvia.

What should I tell my healthcare provider before taking Atelvia?

Before you take Atelvia, tell your healthcare provider if you:

- Have problems swallowing
- Have stomach or digestive problems
- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems
- Have been told you have trouble absorbing mineral in your stomach or intestines (malabsorption syndrome)
- Are pregnant or plan to become pregnant. It is not known if Atelvia can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if Atelvia passes into your breast milk and may harm your baby. You and your doctor should decide if you will take Atelvia or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Certain medicines may affect how Atelvia works.

Especially tell your doctor if you take:

- Actonel® or other medicines to treat osteoporosis
- calcium supplements
- antacids
- laxatives
- iron supplements

Ask your doctor or pharmacist for a list of these medications, if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Atelvia?

- Take Atelvia exactly as your doctor tells you.
- Take Atelvia 1 time a week **right after breakfast**. Choose a day of the week to take Atelvia that best fits your schedule.
- Take Atelvia with at least 4 ounces (about 1-half cup) of plain water.
- Swallow Atelvia tablets whole. **Do not chew, cut, or crush** Atelvia tablets before swallowing. If you cannot swallow Atelvia tablets whole, tell your doctor. You may need a different medicine.

After swallowing Atelvia wait at least 30 minutes:

- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take Atelvia.

If you miss your weekly Atelvia dose, take Atelvia the morning after you remember then return to your normal schedule. Do not take 2 doses at the same time.

You should take calcium and vitamin D as directed by your doctor.

If you take too much Atelvia, call your doctor. Do not try to vomit. Do not lie down.

What are the possible side effects of Atelvia?

Atelvia may cause serious side effects**:**

- See **“What is the most important information I should know about Atelvia”**.

The most common side effects of Atelvia include:

- diarrhea
- flu-like symptoms
- muscle pain

- back and joint pain
- upset stomach
- stomach area (abdominal) pain

You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.
Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of Atelvia. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Atelvia?

- Store Atelvia between 68° F to 77° F (20° C to 25° C).

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

General information about the safe and effective use of Atelvia

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use Atelvia for a condition for which it was not prescribed. Do not give Atelvia to other people, even if they have the same symptoms you have. It may harm them.
This Medication Guide summarizes the most important information about Atelvia. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Atelvia that is written for health professionals.
For more information, go to www.atelvia.com or call 1-800-521-8813.

What are the ingredients in Atelvia?

Active ingredient: risedronate sodium
Inactive ingredients: Edetate disodium, ferric oxide yellow, magnesium stearate, methacrylic acid copolymer, polysorbate 80, silicified microcrystalline cellulose (ProSolv SMCC90), simethicone, sodium starch glycolate, stearic acid, talc, and triethyl citrate.
This Medication Guide has been approved by the U.S. Food and Drug Administration.
Manufactured by:
Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814
Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813
0979G017
Covered under one or more of U.S. Patent Nos. 5,583,122; 5,622,721; 7,645,459 B2 and 7,645,460 B2, and other patents pending.