Bisphosphonates in Osteoporosis Monograph
June 2010

INTRODUCTION:

Purpose:
The purpose of this review is to provide review of available information regarding the bisphosphonates class of medications for consideration of inclusion to the Indian Health Service (IHS) National Core Formulary (NCF). The objective of this monograph is to assimilate available and current medical information to aid the IHS National Pharmacy and Therapeutics Committee's (NPTC) in making a clinical recommendation based upon the body of available clinical evidence. The focus of this review will be associated with the use of bisphosphonates for the treatment and/or prevention of osteoporosis.

Currently there are eight bisphosphonates commercially available in the United States. Four of these products (etidronate, pamidronate, tiludronate and zoledronic acid (oral)) do not carry an indication for osteoporosis therefore these products will only briefly be discussed.

Table 1. Brand and generic names of available bisphosphonates in the United States[1-8]

Brand name	Fosamax®	Didronel®	Boniva®	Aredia®	Actonel®	Skelid®	Reclast®	Zometa®
Generic Name	*Alendronate	Etidronate	*Ibandronate	Pamidronate	*Risedronate	Tiludronate	*Zoledronic acid	Zoledronic acid

*** FDA Indicated for Osteoporosis**

Osteoporosis:[9]
Osteoporosis is a costly public health concern that affects about 55% of the population $\geq$ 55 years old. All ethnic groups are at risk for osteoporosis. However, Caucasians, Asians, and Hispanics tend to be at a higher risk. Females are also more likely than males to develop osteoporosis. In 2005, it was reported that 19 billion health care dollars were spent treating osteoporosis related fractures. In patients that suffered from osteoporosis related fractures, the wrist, spine and hips were common sites for fractures to occur due to low bone mass and structural deterioration of bones. When a fracture occurs in the hip or spine, patients may require extended hospital stays along with a lengthy rehabilitation.

Pathophysiology:[10-11]
Bone maintenance is a continual process in which resorption must be balanced with the deposition of new minerals. If this balance is not maintained, then osteoporosis may develop. Various factors can cause the loss of bone density. Some factors that put an individual at risk are estrogen deficiency, increased age, and/or certain medications.

Estrogen deficiency can cause an increase in the amount of bone loss relative to the amount of new minerals deposited for bone growth. On a molecular level, two types of cells participate in the build up and breakdown of bones. Osteoblasts are cells that form bone while osteoclasts are

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responsible for bone resorption. Estrogen is thought to have a direct effect on the balance of bone formation and resorption. Estrogen acts on specific proteins and receptors found on the osteoblasts and osteoclasts. Estrogen stimulates cell receptors, which cause an increased amount of osteoblast activity. Estrogen also interferes with communication of osteoclast and osteoblast.

Age related factors that put individuals at risk are associated with a decrease in estrogen production after menopause. Increasing age and the associated decrease in bone density can also be attributed to an increase in bone resorption and osteocyte apoptosis. Other factors that contribute to loss of bone density and increase in fracture risk are: comorbid conditions, cognitive impairment, certain medications, deconditioning, inadequate calcium intake, and inadequate intake and absorption of vitamin D.

PHARMACOLOGY/PHARMACOKINETICS:

The action of bisphosphonates on bone tissue is based on their affinity for hydroxyapatite, which is part of the mineral matrix of bone. Bisphosphonates inhibit osteoclast activity and reduce bone resorption and turnover. In postmenopausal women, they reduce the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.[1-8]

Bisphosphonates, however administered, localize strongly to the bone surface, with uptake particularly high at sites of increased bone turnover. Osteoclasts take up bisphosphonates from resorption lacunae in the bone matrix, and the bisphosphonates then trigger the osteoclasts to undergo apoptosis. Aminobisphosphonates, such as pamidronate, zoledronic acid, and ibandronate, interfere with the metabolism of mevalonate, which, among other actions, is essential for the biosynthesis of cholesterol and its derivatives.[12]

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Table 2. Pharmacokinetic Properties of Bisphosphonates[1-8]

Product	**A**bsorption	**D**istribution	**M**etabolism	**E**xcretion
Alendronate (Fosamax)	* *F* = (FM=0.64%) (M=0.59%) on empty stomach 2 hours prior to breakfast * 40% decreased *F* if taken within 0.5-1 hour before breakfast * Studies show still effective if taken 30 min before breakfast	* SS VOD, exclusive to bone = 28 L * Protein Binding = 78%	Not Metabolized	* Terminal half-life = exceeds 10 years * Renal Clearance = 71 ml/min
Etidronate (Didronel)	* *F* = 3%	NA	Not Metabolized	* Plasma half-life = 1-6 hours
Ibandronate (Boniva)	* *F* = 0.6% no * No meaningful reduction in bioavailability when ibandronate is taken at least 60 minutes before breakfast	* Terminal VOD = 90 L * Protein Binding= 85.7-99.5% increasing with increased serum conc[1]entrations	Not Metabolized	* Terminal half-life = 37-157 hours * Renal Clearance = 61 ml/min
Pamidronate (Aredia)	NA		Not Metabolized	
Risedronate (Actonel)	* *F* = 0.63% * Dosing 0.5 hours prior to breakfast = 55% decrease in *F* * Dosing 1 hour prior to breakfast = 30% decrease in *F* * Studies show still effective if taken 30 min before breakfast	* SS VOD = 13.8 L/kg * Protein Bi[7-8]nding = 24%	Not Metabolized	* Terminal half-life = 561 hours * Renal Clearance = 52 ml/min
Tiludronate (Skelid)	* *F* = 6% in healthy males	* Protein Binding = 90%	Not Metabolized	* Renal Clearance = 10

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				ml/min
Zoledronic Acid (Reclast) (Injection)		* Protein Binding = 28-53% increasing with higher plasma concentrations	Not Metabolized	* Terminal half-life = 146 hours
Zoledronic Acid (Zometa) (Injection)		* Protein Binding = 28-53% increasing with higher plasma concentrations	Not Metabolized	* Terminal half-life = 146 hours

FDA APPROVED INDICATIONS:[1-8]

Alendronate Sodium

1. Treatment and prevention of osteoporosis in postmenopausal women
2. Treatment to increase bone mass in men with osteoporosis
3. 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
4. Treatment of Paget's disease of bone in men and women

Etidronate Disodium

1. Treatment of symptomatic Paget's disease of bone
2. Treatment and prevention of heterotopic ossification following total hip replacement or due to spinal cord injury.
3. **Etidronate is NOT approved for osteoporosis**.

Ibandronate Sodium

Treatment and Prevention of Postmenopausal Osteoporosis

Pamidronate Disodium

1. Hypercalcemia of Malignancy
2. Paget's Disease
3. Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma
4. **Pamidronate is NOT approved for osteoporosis**

Risedronate Sodium

1. Treatment and prevention of osteoporosis in postmenopausal women
2. Treatment to increase bone mass in men with osteoporosis

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3. 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
4. Treatment of Paget's disease of bone in men and women

Tiludronate Disodium

1. Treatment of Paget's disease of bone
2. **Tiludronate is NOT approved for osteoporosis**

Zoledronic Acid

1. Treatment and prevention of osteoporosis in postmenopausal women
2. Treatment to increase bone mass in men with osteoporosis
3. 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.
4. Treatment of Paget's disease of bone in men and women

Zoledronic Acid

1. Treatment of hypercalcemia of malignancy
2. Treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy
3. **Zometa is NOT approved for osteoporosis**

CURRENT NATIONAL CORE FORMULARY ALTERNATIVES:[13]

The IHS National Core Formulary has **ANY** oral bisphosphonate listed.

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DOSAGE AND ADMINISTRATION:[1-8]

Table 3 Dosage and administration based upon FDA approved indications

INDICATION	Alendronate	Ibandronate	Risedronate	Zoledronic Acid
Treatment of Postmenopausal Osteoporosis	*one 70 mg tablet once weekly or *one bottle of 70 mg oral solution once weekly or *one 10 mg tablet once daily	*one 150 mg tablet taken once monthly *one 2.5 mg tablet taken once daily	*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	*5 mg infusion once a year given intravenously over no less than 15 minutes
Prevention of Postmenopausal Osteoporosis	*one 35 mg tablet once weekly or *one 5 mg tablet once daily	*one 150 mg tablet taken once monthly *one 2.5 mg tablet taken once daily	*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	*5 mg infusion given once every **2 years** intravenously over no less than 15 minutes

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Treatment to Increase Bone Mass in Men with Osteoporosis	*one 70 mg tablet once weekly or *one bottle of 70 mg oral solution once weekly or *one 10 mg tablet once daily	**Not Indicated**	* one 35 mg tablet orally, taken once a week	*5 mg infusion once a year given intravenously over no less than 15 minutes
Treatment and Prevention of Glucocorticoid-Induced Osteoporosis	**Tx Only:** 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	**Not Indicated**	* one 5 mg tablet orally, taken daily	*5 mg infusion once a year given intravenously over no less than 15 minutes
Treatment of Paget's Disease	40 mg once a day for six months	**Not Indicated**	* 30 mg orally once daily for 2 months	*5 mg infusion once a year given intravenously over no less than 15 minutes

GUIDELINES:

National Osteoporosis Foundation[11]:

The NOF offers a review of several of the FDA-approved pharmacological agents for the treatment of osteoporosis in their 2010 revision. The guidelines primarily focus on prevention, diagnostics, and treatment of osteoporosis in postmenopausal women and men 50 years and older. Bisphosphonates are discussed individually in detail. The guidelines report that the side effect profiles are very similar for oral bisphosphonates, which include difficulty swallowing, esophagitis, gastric ulcer, and osteonecrosis of the jaw in rare instances. In clinical trials, it appears that patients receiving zoledronic acid may be at an increased risk of atrial fibrillation when compared to placebo. This risk is not known with other bisphosphonates.

The North American Menopausal Society (NAMS)[14]

In their 2010 position statement for management of osteoporosis in post menopausal women, NAMS recommends that medication therapy for osteoporosis be initiated in all post menopausal women who:

- Had an osteoporotic vertebral or hip fracture, or

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- Have BMD values consistent with osteoporosis (T-scores ≤ -2.5) at the lumbar spine, femoral neck, or total hip region, or
- Have T-scores from -1.0 to -2.5 and a 10-year risk, based on the FRAX calculator, of major osteoporotic fracture of ≥ 20% or of hip fracture of ≥ 3%

NAMS recognizes bisphosphonates as the first-line medication for postmenopausal women with osteoporosis. NAMS did not identify a specific duration of therapy other than it should be for long term in most women, and decisions to discontinue or suspend therapy should be based on the women's risk of fracture and her response to treatment.

Journal of Obstetrics and Gynaecology Canada (JOGC) [15]

In their 2009 update, JOGC recommended "treatment with alendronate, risedronate, or zoledronic acid should be considered to decrease the risk of vertebral, non-vertebral, and hip fractures" (level 1A recommendation). They also recommend that "etidronate is a weak antiresorptive agent and may be effective in decreasing the risk of vertebral fracture in those at high risk" (level 1B recommendation). It should be noted that ibandronate was not addressed in their write up. JOGC makes no specific recommendation for one product (with an FDA-approved indication) over another.

American College of Physicians (ACP) Clinical Practice Guidelines[16]

In 2008, ACP evaluated evidence from 24 meta-analyses and 35 additional randomized trials comparing the effects of bisphosphonates (alendronate, risedronate, and etidronate), calcitonin, raloxifene, estrogen, teriparatide, calcium and vitamin D on fracture incidence. They also evaluated 14 other articles comparing ibandronate, pamidronate, zoledronic acid, and tamoxifen.

There is insufficient evidence to support superiority of one bisphosphonate over another; except ibandronate, which did not show a reduction in non-vertebral fracture in a large trial. Although the guidelines do not recommend one bisphosphonate over another, the evidence available shows that bisphosphonates, in general, reduce vertebral, non-vertebral, and hip fracture risk. The guidelines consider these agents as reasonable first line pharmacologic options, especially in patients at high risk for hip fracture. Evidence was deemed insufficient to determine duration of therapy.

Institute for Clinical Systems Improvement Health Care Guideline (ICSI)[17]

ICSI made several recommendations in their 2008 update:

- Recommendations based on level 1 evidence: "Excellent clinical trial data based on BMD and biomarkers supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal low bone density osteopenia or osteoporosis. The best clinical trials have been done with alendronate, risedronate and ibandronate." "Good clinical trial data support the use of alendronate for preventing bone loss in men diagnosed with osteoporosis."

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- Recommendations based on level 2 evidence: "Clinical trial data supports the use of oral bisphosphonates for reducing bone loss in men and women diagnosed with glucocorticoid-induced bone loss."
- Recommendations based on level 3 evidence: "Clinical trial data suggests that oral bisphosphonates may reduce fracture risk in men and women diagnosed with glucocorticoid-induced bone loss."

ICSI makes no specific recommendation for preference between alendronate, risedronate, or ibandronate.

American College of Obstetrics and Gynecologists (ACOG)[18]

The 2004 ACOG practice bulletin reviewed several treatment strategies for treating osteoporosis, including estrogen therapy, bisphosphonates (alendronate and risedronate), selective estrogen receptor modulators (SERMS), calcitonin, and parathyroid hormone (PTH). The guidelines also assessed the benefit of using bisphosphonates in combination with other treatment agents.

Although combination therapies of bisphosphonates plus estrogen and bisphosphonates plus raloxifene have demonstrated small increases in bone mineral density (approximately 1-3% in 2 years for both combinations), the significance of this impact on fracture risk reduction is unknown. Long-term data with combination therapy has not been evaluated, and would inherently result in increased costs. Based on available evidence, ACOG recommends that bisphosphonates, along with raloxifene, calcitonin, and PTH, be considered among the first line pharmacological agents for osteoporosis treatment.

American Association of Clinical Endocrinologists Medical Guidelines (AACE)[16]

In their 2003 update, AACE recommends that when pharmacotherapy is indicated, the first priority is "agents approved by the US Food and Drug Administration (FDA) for the prevention or treatment (or both) of osteoporosis". The second priority recommendation is "agents that are not approved by the FDA but for which level 1 or level 2 evidence of efficacy and safety is available (these agents are appropriate for patients who are unable to take approved agents or who have complex and extenuating medical problems that preclude the effective use of approved agents)". It should be noted that, at this time, the only FDA-approved bisphosphonates for the prevention/treatment of osteoporosis were alendronate and risedronate (etidronate and pamidronate had "off label" use for patients with osteoporosis). AACE makes no specific recommendation for either alendronate or risedronate.

EFFICACY:

Alendronate:

There are four key trials and a meta-analysis that will be discussed to provide clinical trial data for alendronate use.

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Liberman et.al published results from a randomized, placebo-controlled trial that assessed the effect of alendronate on BMD, the incidence of fractures, height loss and adverse effects. This study randomized 994 postmenopausal women (age 45-80 years) with osteoporosis (BMD at least 2.5 SD below the mean) to placebo or alendronate (5 or 10mg daily for 3 years or 20mg for 2 years followed by 5mg for 1 year). All patients received 500mg elemental calcium each day. BMD in women receiving 10mg daily alendronate was significantly improved across each measurement site (P<0.001 for all). A 48% reduction was seen in new vertebral fractures (3.2% versus 6.2%, P=0.03). Additionally, alendronate decreased the progression of vertebral deformities (33% vs. 41%, P=0.028) and reduced loss of height (P=0.005). Alendronate was well tolerated in this study.[19]

In 1996, Black and colleagues published the results from the Fracture Intervention Trial (FIT) I trial. [20] This study enrolled 2027 postmenopausal women aged 55-81 with a low femoral neck BMD. Patients were randomized to receive placebo or alendronate (5mg daily, increased to 10mg at 24 months) and followed for 36 months. Of note, all patients with less than 1000mg daily calcium intake received 500mg elemental calcium plus 250 IU vitamin D. The primary endpoint was new vertebral fractures upon radiography. Compared with placebo, the alendronate group had a 47% RRR (RR 0.53, 95% CI 0.41-0.68). The "any clinical fracture" (a secondary endpoint) showed a relative hazard of 0.72 (95% CI 0.58-0.90), with relative hazards for hip fracture and wrist fracture of 0.49 (95% CI, 0.23-0.99) and 0.52 (95% CI, 0.31-0.87) respectively. Adverse effects were also analyzed and were not significantly different than placebo. Based upon these data, it appears alendronate was well tolerated and reduced both new vertebral fractures and other clinical fractures.

The 1998 FIT II trial was a randomized, blinded, placebo-controlled trial that evaluated 4432 women aged 54 to 81 years old with low femoral neck BMD. [21] This 4-year trial focused on women with no history of vertebral fractures. Similar to other studies, all patients reporting less than 1000mg per day of calcium were given 500mg of elemental calcium and 250 IU vitamin D supplements. Patients were randomized to receive either placebo or 5mg per day alendronate for 2 years (dose was increased to 10mg per day for the remainder based upon results of other published trials and alendronates effect on BMD.) Primary outcomes included x-ray confirmed clinical fractures, new vertebral deformities detected by morphometric measurements on radiographs and BMD. Findings included a statistically significant increase in BMD across all points (P< 0.001). There was a trend for reduced clinical fractures 14% reduction (RH 0.86, 95% CI 0.73-1.01), but a significant 36% reduction in clinical fractures with patients with a low BMD (femoral neck >2.5 SD below normal young adult mean; RH 0.64, 95% CI 0.5-0.82).

In 2006, the Fracture Intervention Trial Long-term Extension (FLEX) results were published. [22] This trial was a randomized, double-blind trial was an extension of the FIT trials and was designed to assess the effect on BMD of continuing alendronate 5 or 10mg per day for 10 years or discontinuing after 5 years (n=1099). The primary outcome was total hip BMD with other site BMD and bone remodeling markers as secondary endpoints. Patients switched to placebo for 5 years saw total hip BMD decline (-2.4%; 95% CI -2.9-1.8%; p<0.001) and spine BMD (-3.7%; 95% CI -4.5-3.0%; p<0.001), but remained at or above pretreatment levels. Patients who received placebo had increased serum markers of bone turnover and saw no significant risk of

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nonvertebral fracture (RR, 1.00; 95% CI 0.76-1.32). This trial suggest that patients show modest decline in BMD and a rise in bone markers after 5 years and that "discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk"

A 2008 Cochrane review described the efficacy of alendronate for both primary and secondary prevention of fractures in postmenopausal women. This meta-analysis reviewed 11 trials including 12,068 women on alendronate versus placebo at a dose of 10mg per day for at least 1 year with an outcome of incidence of fracture. The data for vertebral fractures revealed a 45% RRR (combined RR 0.55, 95% CI 0.45-0.67; primary prevention, RR 0.55, 95% CI 0.38-0.80; secondary prevention, RR 0.55, 95% CI 0.43-0.69). For non-vertebral fractures, combined data reveal a 16% RRR (RR 0.84, 95% CI 0.74-0.94). When separated, the secondary prevention yielded a 23% RRR (RR 0.77, 95% CI 0.64-0.92) while primary prevention data was not statistically significant (RR 0.89, 95% CI 0.76 to 1.04). This analysis also identified secondary prevention of hip fracture (RRR 53%, RR 0.47, 95% CI 0.26-0.85) and wrist fracture (50% RRR, RR 0.50, 95% CI 0.34-0.73). Based upon these findings, the authors concluded that statistically significant reductions of vertebral, non-vertebral, hip and wrist fractures for secondary prevention and statistically significant reductions for primary prevention of vertebral fracture.[23] It should be noted that this meta-analysis focused on 10mg per day dosage only.

Ibandronate:

The 2004 Intermittent Regimen intravenous Ibandronate Study (IRIS) studied 520 postmenopausal women with osteoporosis in a randomized, double-blind, placebo-controlled fashion.[24] Similar to most bisphosphonates studies, patients received supplemental calcium (500mg) and vitamin D (400 IU). Patients received 1 or 2 mg ibandronate or placebo every 3 months and the primary endpoint was change in lumbar spine BMD after 1 year with a secondary endpoint of proximal femur BMD. This study found that both the 1 and 2mg ibandronate improved lumbar spine and hip BMD, with the 2 mg providing the greatest benefit and was well tolerated. Of note, this article utilized the injectable ibandronate, which is not approved in the United States.

Also in 2004, Chestnut and colleagues published the results of a randomized, double-blind, placebo-controlled trial that compared fracture rates in postmenopausal women treated with ibandronate.[25] The primary endpoint was new vertebral fractures at 3 years with secondary endpoints of new vertebral fractures at 1 and 2 years and non-vertebral fractures at 3 years. Patients were randomized to receive 2.5mg daily, intermittent therapy with 20mg every other day for 12 doses repeated every 3 months, or placebo. There was a significant reduction of new morphometric vertebral fractures in the daily and intermittent groups (62%, p=0.0001; 50%, p=0.0006) compared to placebo at 3 years. Significant reductions in new vertebral fractures were seen at 2 years (61%, p=0.0006; 56%, P=0.0017). No significant reductions were seen at 1 year or for non-vertebral fractures.

In an article published by Delmas et al. in 2006, injectable ibandronate in 2 different regimens (2mg every 2 months and 3mg every 3 months) was compared to an oral regimen (2.5mg daily).[26] This study was a randomized, double-blind, double-dummy, noninferiority trial of 1395

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postmenopausal women with osteoporosis with a primary end-point of lumbar spine BMD change at 1 year. Hip BMD, serum C-telopeptide of type I collagen (CTX) and safety and tolerability were also studied. The IV ibandronate regimens were considered noninferior to the oral regimen with reductions in lumbar BMD of 5.1%, 4.8% and 3.8% for the 2mg IV every 2 months, 3mg IV every 3 months and 2.5mg oral daily. Hip BMD increases were greater with the IV treatment groups as well as CTX level reductions. Based upon the findings of this noninferiority trial, IV ibandronate in the studied regimens are a least as effective as ibandronate 2.5mg orally daily.

The MOBILE (Monthly Oral iBandronate in LadiEs) study compared once monthly and once daily regimens of ibandronate with the primary endpoint being lumbar spine BMD change at 1 year and secondary endpoints of 2 year change in BMD at the lumbar spine and proximal femur and change in CTX. This study was a 2 year, randomized double blind, parallel non-inferiority trial of postmenopausal women with osteoporosis with patients receiving ibandronate "2.5mg daily, 50 + 50mg once-monthly (single doses given on 2 consecutive days), 100mg once-monthly or 150mg once-monthly."[27] Monthly regimens were at least as effective as the daily regimen with BMD changes of 3.9%, 4.3%, 4.1% and 4.9% at 1 year and5%, 5.3%, 5.6% and 6.6% at 2 years.[27-28] Serum CTX decreases were seen in all arms. Additionally, ibandronate was well tolerated across all treatment arms.

The 3 year extension of MOBILE was published by Stakkestad et al. in 2008.[29] Patients who completed MOBILE were eligible to receive either 100mg or 150mg month oral ibandronate. The 3 year post-hoc analysis revealed lumbar BMD improvements of 7.6% (150mg monthly, $p<0.0001$ vs. baseline) and 6.4% (100mg monthly, $p<0.0001$ vs. baseline). Patients also demonstrated improved total hip BMD and serum CTX levels. These data suggest 150mg monthly ibandronate is a good option for improvement of BMD over a period of 3 years.

Risedronate:

The 1998 article published by Mortensen et al. discussed the double-blind, placebo-controlled study on the use of risedronate in early menopausal patients with normal BMD.[30] Patients had normal bone mass and were randomized to receive either placebo, risedronate 5mg daily or risedronate 5mg cyclically (daily for 2 weeks, off for 2 weeks) for 2 years on and 1 year off treatment. After year 1, patients could stop the study, complete year 2 without therapy or continue an additional year of study with 1 year off treatment. The primary end point was percent change in lumbar spine BMD at 2 years with femoral neck BMD and markers of bone turnover as secondary endpoints. At 2 years, an increase in lumbar spine BMD was seen in the risedronate 5mg daily group versus placebo (5.7% vs. 1.4%) and decreases in the risedronate 5mg cyclical regimen (1.6% vs. 4.3%). Hip bone mass increased at 2 years compared to placebo (5mg daily, 5.4%; 5mg cyclical, 3.3%). Of note, this trial only looked at surrogate markers and did not include fracture data.

In 1999, an article was written by Harris et al. to discuss results from the Vertebral Efficacy with Risedronate Therapy (VERT) study (results from patients treated in 1 of 110 centers in North America).[31] The VERT trial was a randomized, double-blind, placebo-controlled trial of

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postmenopausal women with at least 1 vertebral fracture. It was designed to assess efficacy of daily risedronate to reduce vertebral and other fractures and change in BMD from baseline. Patients received 2.5mg daily, 5mg daily or placebo and were followed for 3 years. The 2.5mg arm was discontinued after 1 year due to modification of the study protocol as data from other trials showed 2.5mg being less effective than 5mg. With the 5mg daily regimen, new vertebral fractures showed a 41% RRR (95% CI, 18-58; 11.3% vs. 16.3%, P=0.003). The cumulative data at 3 years for nonvertebral fractures showed a 39% RRR (95% CI, 38%-81%; 5.2% vs. 8.4%, p=0.02). Data from BMD showed significant increases at the lumbar spine, femoral neck, femoral trochanter and midshaft of the radius. Safety data was similar to placebo.

Reginster and colleagues published an article in 2000 describing findings from the VERT trial in patients treated at 80 study centers in Europe and Australia. [32] Study design was discussed above. Risedronate 5mg daily showed a 49% RRR at 3 years (p<0.001) for new vertebral fractures. A non-statically significant reduction of 33% (p=0.06) versus placebo was seen at 3 years.

McClung and colleagues published results from the Hip Intervention Program (HIP) study in 2001.[33] This study focused on the effects of risedronate on occurrence of hip fracture and was a multi-national randomized clinical trial that included 5445 women aged 70-79 years old with osteoporosis (T score<-4 or <3 with 1 risk factor for hip fracture) and 2886 women ≥ 80 with at least 1 nonskeletal risk factor or low femoral neck BMD. Patients received 2.5 mg daily, 5mg daily or placebo for 3 years. The primary end point was occurrence of hip fracture. In the combined data, hip fracture was noted in 2.8% of women receiving risedronate compared to 3.9% receiving placebo (RR 0.7; 95% CI 0.6-0.9, p=0.02). The 70-79 year old group receiving risedronate had a 1.9% occurrence of hip fracture versus 3.2% on placebo (RR 0.6, 95% CI 0.4-0.9, p=0009). It was noted that the >80 year old group did not have a statistical difference between risedronate and placebo (4.2% vs. 5.1%, p=0.35).

A 2008 Cochrane meta-analysis described the efficacy of risedronate for both primary and secondary prevention of fractures in postmenopausal women. This articled reviewed data from 7 clinical trials that included 14,049 women on risedronate 5mg daily for at least 1 year comparing to either placebo, calcium/vitamin D or both. The data for primary prevention showed no statistically significant effect on fractures. Data for secondary prevention showed a 39% RRR in vertebral fracture (RR 0.61, 95% CI 0.5-0.76) and a 20% RRR (RR 0.8, 95% CI 0.72-0.90) for non-vertebral fractures. Hip fracture showed a 26% RRR (RR 0.74, 05% CI 0.59-0.94). Based upon these data, the authors concluded, "At 5mg/day a significant and clinically important benefit in the secondary prevention of vertebral, non-vertebral and hip fractures was observed, but not for the wrist." They also concluded, "There were no statistically significant reductions in the primary prevention of vertebral and non-vertebral fractures."[34]

Zoledronic Acid:

A 2002 article from Reid et al. was a randomized, double-blind, placebo-controlled trial of 381 postmenopausal women with low BMD.[35] Patients were randomized to receive placebo, IV zoledronic acid of 0.25mg, 0.5mg or 1mg at three month intervals, 4mg as a single dose or 2mg

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for 2 doses 6months apart. The primary end point for this study was BMD at the lumbar spine. This study saw significant improvements across all zoledronic acid groups compared to placebo. Of note, myalgia and pyrexia were seen more frequently in the zoledronic acid groups but dropout rates were similar to placebo. Of note, this trial focused on surrogate endpoints versus fracture rates.

The Health Outcomes and Reduced incidence with Zoledronic Acid Once Yearly (HORIZON) investigators produced two articles, the HORIZON Pivotal Fracture Trial (PFT) and the HORIZON Recurrent Fracture Trial (RFT).[36-37] In the randomized double-blind, placebo controlled HORIZON PFT[36], 7765 postmenopausal were randomized to receive 5mg zoledronic acid IV or placebo at baseline,12 months and 24 months. This trial's primary endpoint was new vertebral fracture and hip fractures with BMD, bone turnover markers and safety outcomes being secondary endpoints. At 3 years, vertebral fractures were seen in 3.3% zoledronic acid versus 10.9% placebo (RR 0.30, 95% CI 0.24-0.38). Hip fracture data revealed 1.4% zoledronic acid versus 2.5% placebo (RR 0.59, 95% CI 0.42-0.83). There were significant improvements noted in secondary endpoints of BMD across locations as well as with biochemical markers. Overall, adverse events were similar, but it should be noted that a significant increase in serious atrial fibrillation was seen (0.5% placebo vs. 1.3% zoledronic acid, $p<0.001$).

With the HORIZON RFT, Lyles et al., 2127 patients received 5mg IV zoledronic acid or placebo. Patients within this study received an infusion within 90 days of hip fracture repair. Occurrence of new clinical fractures were the primary end point with BMD in the non-fractured hip, new vertebral, nonvertebral, hip fractures and safety being secondary endpoints. Median follow-up time for this trial was 1.9 years. New clinical fracture rate was 8.6% versus 13.9% (zoledronic acid, placebo; HR 0.65, 95% CI 0.50-0.84). Statistically significant improvements were seen in the nonvertebral, vertebral fracture rates (HR 0.73, 95% CI 0.55-0.98; HR 0.54, 95% CI 0.32-0.92) and death (HR 0.72, 95% CI 0.56-0.93). Of note, no statistical difference was seen with hip fracture (HR 0.70, 95% CI 0.41-1.19). Adverse events were similar between groups, but a greater number of patients reported pyrexia, myalgia bone and musculoskeletal pain. Atrial fibrillation and other cardiovascular rates were similar among groups in this study.

Two additional post-hoc analyses of the HORIZON trials were published in 2009 and 2010.[38-39] Eastell and colleagues provided a subgroup analysis that looked at new vertebral and hip fractures, with secondary endpoints of nonvertebral fractures and femoral neck BMD.[38] These data show that zoledronic acid may be more effective in women of younger age, overweight/obese and with normal renal function. In the Boonen et al. analysis of women with recent hip fracture or women $\geq$75 with either T$\leq$2.5 or vertebral or hip fracture, patients had a lower incidence of new clinical fractures. Of note, these were subgroup analyses.

Recent randomized, double-blind placebo-controlled trials were published by Grey et.al[40] and McClung et al.[41] The Grey article sought to determine the "duration of antiresorptive action of a single 5mg dose of IV zolendronate" and looked at bone turnover markers and BMD (lumbar spine, proximal femur and total body) for its analysis. Bone turnover markers and BMD improved significantly and were sustained to at least 2 years. This article utilized a small population and surrogate endpoints for its assessment. McClung et al.[41] also looked at BMD

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and bone turnover markers for their analysis with a focus on percentage change at 2 years. Patients received zoledronic acid 5mg IV at baseline and at month 12, 5mg IV at baseline and placebo at 12 months or placebo at baseline and at 12 months. Lumbar spine BMD improved in both zoledronic acid groups (5.18%, 4.42% and -1.32%; p <0.001). Bone turnover markers were significantly improved with the zoledronic acid groups. These data suggest that a single dose may prevent bone loss for 2 years post infusion.

NICE:[42-43]

In January 2010, the National Institute for Health and Clinical Excellence (NICE) produced ammended reviews for the primary and secondary prevention of osteoporosis. In their reviews, they focused on the use of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparitide (ibandronate and zoledronic acid unavailable at the time of publication). This discussion will focus on recommendations associated with bisphosphonates. This review found that alendronate and risedronate were both effective in reducing vertebral fractures and hip fractures in osteoporotic women.

AHRQ:[44]

Maclean and colleagues published a meta-analysis to compare the effectiveness of treatment options for low bone density or osteoporosis. Its focus was studies that reported fracture information, specifically the rate of or risk for fracture. Adverse effect information was also collected for this analysis and focused on cardiovascular, thromboembolic (raloxifene was included) or upper gastrointestinal events, malignancy and osteonecrosis. Based upon their findings, the authors determined "Good evidence suggests that alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, parathyroid hormone and raloxifene prevent vertebral fractures more than placebo" and that "alendronate, risedronate and estrogen prevent hip fractures more than placebo." They did not suggest relative efficacy between products as they did not identify sufficient evidence.

Head-To-Head Trials:

A 2003 article published by Hosking et al. compared weekly alendronate (70mg), daily risedronate (5mg) and placebo. This randomized, double-blind placebo controlled trial of 549 post menopausal women with a primary endpoint of bone turnover markers at 3 months and spine and hip BMD at 6 and 12 months and 1, 6 and 12 month bone turnover markers as secondary endpoints. Results at 3 months showed greater reduction in markers for alendronate compared to risedronate (-52% vs. -32%, p<0.001). Additionally, statistically significant improvements in BMD were seen with alendronate at the spine (4.8% vs. 2.8%, p<0.001). Hip BMD was significantly greater with alendronate versus risedronate at 6 and 12 months (2.7% vs. 0.9%, p<0.001). Study weaknesses include comparing a weekly product to a daily product as well as the use of surrogate endpoints versus clinical endpoints.[45]

Another head-to-head randomized clinical trial was conducted by Luckey, et al.[46] This 12-month multicenter trial was conducted at 52 sites within the United State to compare alendronate

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70mg/week to raloxifene 60mg/day in postmenopausal osteoporosis. The primary endpoint was the lumbar spine BMD percent change at 12 months. A significantly greater increase in lumbar spine BMD was seen in the alendronate as compared to the raloxifene group (4.4% vs. 1.9%, $P < 0.001$) and the results were seen as early as 6 months into therapy (1.4%; 95% CI: 0.8%, 2.0%, $P<0.001$). Safety data revealed similar outcomes as well as tolerability to treatment. Of note, this study used the BMD marker for efficacy and did not assess fractures.

A head-to-head randomized clinical trial from Recker and colleagues was conducted comparing the effects of alendronate 10mg/day and raloxifene 60mg/day. The primary endpoint was osteoporotic fractures. This multi-site study protocol included ambulatory postmenopausal women between ages 50-80 years with femoral neck T-scores between -2.5 and -4 (modified to -2.0 to -4.0), no prevalent vertebral fractures and no prior treatment with an antiresorptive agent. This trial was terminated early due to the inability to recruit the required treatment naïve women to achieve statistical power. There was insufficient power to compare the risk of fracture between the 2 treatment options. [47]

Results of the Monthly Oral Therapy with Ibandronate for Osteoprosis iNtervention (MOTION) trial were published by Miller and colleagues in 2008.[48] This study was a randomized, double-blind, double-dummy, parallel-group, non-inferiority trial of postmenopausal women with low BMD (T-score < -2.5 and $\geq$ -5.0). Patients were randomized to alendronate 70mg weekly or ibandronate 150mg monthly. Primary endpoints were change in BMD from baseline and 12 months for lumbar spine and total hip. The BMD data at 12 months for the lumbar spine revealed 5.8% (alendronate) versus 5.1% (ibandronate) (95% CI for difference, -1.13, -0.23: non-inferiority met at $\geq$ -1.41) and total hip 2.98% versus 2.82 (95% CI for difference, -0.43, 0.10; non-inferiority condition met at $\geq$ -0.87%). Of note, this trial was a non-inferiority trial and used surrogate endpoints versus clinical endpoints.

Emkey and colleagues published additional results from the MOTION study in their 2009 article.[49] This article was focused on the results of the secondary endpoints (lumbar spine and total hip BMD, bone turnover markers and adverse effects.). Data were similar across these endpoints suggesting similar efficacy of weekly alendronate and monthly ibandronate. As with the Miller article[48], these data represent surrogate endpoints versus clinical data.

The eValuation of iBandronate Efficacy (VIBE) was published by Harris et al. in 2009.[50] The VIBE study was a retrospective observational study using data from pharmacy and medical claims databases in the United States. This study included women $\geq$45 who received either monthly ibandronate or weekly bisphosphonates (alendronate 70mg or risedronate 35mg) without diagnoses of Paget's disease or malignant cancer per database data. Outcomes included first new clinical fractures at the hip, nonvertebral or vertebral. Data revealed no difference in hip fracture, nonvertebral and any clinical fracture between groups, but significantly lower risk of vertebral fracture among patients treated with ibandronate (adjusted RR 0.36, 95% CI 0.18-0.75, p=0.006). Of note, this trial was observational and based on claims data.

ADVERSE EVENTS:[1-8]

Alendronate Sodium (Fosamax)

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Common:

1. **Gastrointestinal:** Abdominal pain, Constipation, Diarrhea, Flatulence, Indigestion, Vomiting (pediatric patients, 29.4%)
2. **Neurologic:** Headache (2.6%)
3. **Other:** Fever (up to 25%), Influenza-like symptoms (up to 25%)

Serious

1. **Dermatologic:** Alopecia, Skin reaction extreme
2. **Gastrointestinal:** Duodenal ulcer disease, Esophageal cancer, Esophageal erosions, With bleeding, Esophageal perforation, Esophageal stricture, Esophagitis (1.5%), Gastric ulcer, Ulcerative pharyngitis, acute, Ulcer of esophagus (1.5%)
3. **Immunologic:** Hypersensitivity reaction
4. **Musculoskeletal:** Arthralgia, Aseptic necrosis of bone, of the jaw (rare), Bone pain, Femur shaft fracture, Low-energy, Myalgia, Subtrochanteric fracture of femur,
5. **Other:** Esophageal cancer

Ibandronate Sodium (Boniva)

Common:

1. **Cardiovascular:** Hypertension (5.3% to 7.3%)
2. **Gastrointestinal:** Abdominal pain (5.1% to 7.8%), Diarrhea (2.4% to 6.8%), Indigestion (3.6% to 11.9%), Nausea (2.1% to 5.1%)
3. **Musculoskeletal:** Backache (4.3% to 13.5%)
4. **Neurologic:** Headache (2.6% to 6.5%)
5. **Respiratory:** Bronchitis (2.1% to 10%), Upper respiratory infection (2% to 33.7%)

Serious

1. **Gastrointestinal:** Duodenal ulcer disease, Esophageal cancer, Esophageal erosions, Esophageal perforation, Esophageal stricture, Esophagitis, Gastric ulcer, Ulcer of esophagus
2. **Musculoskeletal:** Arthralgia (3.5% to 9.6%), Aseptic necrosis of bone, of the jaw, Bone pain (infrequent), Musculoskeletal pain (infrequent), Myalgia (0.8% to 5.7%)

Risedronate Sodium (Actonel)

Common:

1. **Dermatologic:** Rash (osteoporosis, 3 to 4%; Paget's disease, 12%)

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2. **Gastrointestinal:** Abdominal pain (up to 12%), Constipation (12% to 13%), Diarrhea (osteoporosis, 6%; Paget's disease, 20%), Indigestion (7% to 8%), Nausea (6% to 9%)
3. **Neurologic:** Asthenia (4% to 5%)
4. **Other:** Influenza-like illness (7% to 9%)

Serious

1. **Cardiovascular:** Cardiac dysrhythmia (2%), Peripheral edema (4% to 6%)
2. **Dermatologic:** Immune hypersensitivity reaction (rare)
3. **Gastrointestinal:** Esophageal cancer
4. **Musculoskeletal:** Arthralgia (up to 24%), Aseptic necrosis of bone, of the jaw (rare), Bone pain (1% to 5%), Myalgia (5% to 7%)
5. **Renal:** Nephrolithiasis (3%)
6. **Reproductive:** Benign prostatic hyperplasia (5%)
7. **Other:** Esophageal cancer

Zoledronic Acid (Reclast)

Common:

1. **Cardiovascular:** Peripheral edema (Paget's Disease, 3%; osteoporosis, 4.6% to 5.5%; bone metastasis, 21%)
2. **Endocrine metabolic:** Weight decreased (bone metastasis, 16%)
3. **Gastrointestinal:** Abdominal pain (osteoporosis (female), 0.9% to 4.6%; osteoporosis (male), 7.9%; Paget's disease, 2%; hypercalcemia of malignancy, 16%; bone metastasis, 14%), Constipation (Paget's disease, 6%; hypercalcemia of malignancy, 27%; bone metastasis, 31%), Diarrhea (osteoporosis, 5.2% to 6%; Paget's disease, 6%; hypercalcemia of malignancy, 17%; bone metastasis, 24%), Loss of appetite (osteoporosis, 1% to 2%; Paget's disease, 2%; hypercalcemia of malignancy, 9%; bone metastasis, 22%), Nausea (osteoporosis, 4.5% to 8.5%; Paget's disease, 9%; hypercalcemia of malignancy, 29%; bone metastasis, 46%), Vomiting (Paget's disease, 2%; osteoporosis, 3.4% to 4.6%; hypercalcemia of malignancy, 14%; bone metastasis, 32%)
4. **Musculoskeletal:** Arthralgia (osteoporosis (female), 17.9% to 23.8%; osteoporosis (male), 11.1%; hypercalcemia of malignancy, 5% to less than 10%; Paget's disease, 9%; bone metastasis, 21%), Backache (Paget's disease, 4%; bone metastasis, 15%)
5. **Neurologic:** Asthenia (osteoporosis, 3.2 to 5.3%; Paget's disease, 2%; bone metastasis, 24%), Dizziness (osteoporosis, 2% to 7.6%; Paget's disease, 9%; bone metastasis, 18%), Headache (osteoporosis (female), 3.9% to 12.4%; osteoporosis (male), 15%; Paget's disease, 11%; hypercalcemia of malignancy, 5% to less than 10%; bone metastasis, 19%), Insomnia (hypercalcemia of malignancy, 15%; bone metastasis, 16%), Paresthesia (Paget's disease, 2%; bone metastasis, 15% .)
6. **Renal:** Nephrotoxicity (bone metastasis, 11% to 17%)

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7. **Other:** Fatigue (osteoporosis (female), 2.1% to 5.4%; osteoporosis (male), 17.6%; Paget's disease, 8%; bone metastasis, 39%), Fever (osteoporosis (female), 7% to 18%; osteoporosis (male), 15.7%; Paget's disease, 3% to 11%; hypercalcemia of malignancy, 44%; bone metastasis, 32%)

Serious

1. **Cardiovascular:** Atrial fibrillation (1.3% to 2.8%), Cerebrovascular accident (osteoporosis, 2.3%)
2. **Musculoskeletal:** Aseptic necrosis of bone, of the jaw (various malignancies, 28%, 38% and 63%), Bone pain (osteoporosis, 3.2% to 5.8%; Paget's disease, 9%; hypercalcemia of malignancy, 12%; bone metastasis, 55%), Myalgia (osteoporosis (female), 4.9% to 11.7%; osteoporosis (male), 19.6%; Paget's disease, 7%; bone metastasis, 23%)
3. **Respiratory:** Dyspnea (Paget's disease, 5%; osteoporosis (male), 6.5%; hypercalcemia of malignancy, 22%; bone metastasis, 27%)

PRECAUTIONS/CONTRAINDICATIONS:[1-8]

Alendronate Sodium

Precautions:

- Active upper gastrointestinal disease (e.g., dysphagia, esophageal diseases, dysphagia, duodenitis, gastritis, ulcers); may exacerbate condition
- Cancer diagnosis; increased risk of osteonecrosis of the jaw
- Comorbid Barrett's esophagus; avoid use due to risk of esophageal cancer
- Comorbid disorders (e.g., periodontal and/or other preexisting dental disease, anemia, coagulopathy, infection, ill-fitting dentures); increased risk of osteonecrosis of the jaw
- Concurrent therapies (e.g., corticosteroids or chemotherapy); increased risk for osteonecrosis, especially in the jaw
- Dental procedures, invasive (i.e., tooth extraction, dental implants, boney surgery); increased risk of osteonecrosis of the jaw; discontinuing therapy may reduce risk
- Esophageal adverse events, including bleeding and esophageal stricture or perforation, have been reported; discontinue if symptoms develop
- Mental disabilities; preventing understanding of proper administration may lead to increased risk of severe esophageal adverse events
- Mineral metabolism disturbance, such as vitamin D deficiency; should be corrected prior to alendronate administration
- Musculoskeletal pain, severe; has been reported within days, months, or years following therapy initiation; consider discontinuing bisphosphonates if symptoms occur

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- Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection with delayed healing, has been reported
- Poor oral hygiene; increased risk of osteonecrosis of the jaw
- **FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance < 35 mL/min)**

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**
- Patients at increased risk of aspiration should not receive FOSAMAX oral solution.
- Hypersensitivity to any component of this product
- Hypocalcemia; resolve hypocalcemia prior to beginning therapy

Ibandronate Sodium

Precautions:

- **Boniva is not recommended for use in patients with severe renal impairment (creatinine clearance of < 30 mL/min)**
- Additional precautions are the same as Fosamax

Contraindications:

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for **at least 60 minutes**
- Hypocalcemia; resolve hypocalcemia prior to beginning therapy
- Known hypersensitivity to BONIVA or to any of its excipients

Risedronate Sodium

Precautions:

- **Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min)**
- Additional precautions are the same as Fosamax

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**
- Hypocalcemia; resolve hypocalcemia prior to beginning therapy
- Known hypersensitivity to any component of this product

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Zoledronic Acid (Reclast)

Precautions:

- Hypocalcemia must be corrected before initiating therapy
- **Reclast should not be used in patients with severe renal impairment (creatinine clearance < 35 mL/min) due to lack of adequate clinical experience in this population**
- Discontinue use if severe Musculoskeletal Pain occurs
- Osteonecrosis of the jaw (ONJ)
- Reclast should not be used during pregnancy

Contraindications:

- Hypersensitivity to any component of this product
- Hypocalcemia

LOOK-ALIKE/SOUND-ALIKE ERROR RISK POTENTIAL:[51]

Actonel-Actos

Alendronate-risedronate

Aredia-Adriamycin, Meridia

Etidronate-etidocaine, etomidate, etretinate

Fosamax-Flomax, Fosamax Plus D, fosinopril, Zithromax

Pamidronate-papaverine

Skelid-Skaelud (Denmark)

Zometa-Zofran, Zoladex

DRUG INTERACTIONS:[1-8]

- Alendronate Sodium
  - Calcium supplements/antacids- decrease the absorption of alendronate **(Minor severity per Micromedex)**
  - Aspirin- Clinical studies show that daily aspirin and daily alendronate above 10 mg/day increases the incidence of upper GI adverse events

- Ibandronate Sodium

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- Multivalent cations (such as aluminum, magnesium, iron, and calcium) 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 (**Moderate severity per Micromedex)**
- Aspirin warning also evident

- Risedronate Sodium

  - Calcium **(Moderate severity per Micromedex)**
  - Antacids **(Minor severity per Micromedex)**
  - **Aspirin/NSAID-GI adverse event was not evident in trials**

- Zoledronic Acid (Reclast)

  - Concurrent use of thalidomide and zoledronic acid may result in increased risk of renal dysfunction **(Moderate severity per Micromedex)**
  - Renal impairment has been observed following the administration of zoledronic acid in patients with pre-existing renal compromise. In patients with renal impairment, the exposure to concomitant medications that are primarily renally excreted (e.g., digoxin) may increase.
  - **No GI adverse effects**

CONCLUSIONS:

There is good evidence so suggest that bisphosphonates available within the United States:

- Prevent hip fractures
- Prevent other nonvertebral fractures
- Prevent vertebral fractures

It appears that there is a good degree of interchangablility between products. It does not appear from the body of literature, that one product has been proven superior to other products within this class.

RECOMMENDATIONS:

Based upon the information presented within this document, it appears that while there are minor variances between products, one could consider products to be relatively equivalent. Therefore, a consideration could be made for naming a specific product within this class based upon both the clinical, pharmacoeconomic and utilization data for the Indian Health Service.

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