National PBM Drug Monograph
Zoledronic Acid (Zometa)
VHA Pharmacy Benefits Management Strategic Healthcare Group
And The Medical Advisory Panel

GENERIC NAME: Zoledronic Acid

PROPRIETARY NAME/MANUFACTURER: Zometa® (Novartis Pharmaceutical Company).

INTRODUCTION:

Zoledronic acid (also known as zoledronate), a third-generation bisphosphonate, is an intravenous, heterocyclic nitrogen-containing bisphosphonate. [3] During clinical trials in patients with hypercalcemia of malignancy, the response to zoledronic acid was significantly higher when compared to pamidronate. In prostate cancer patients with bone metastases and rising PSA's while on hormonal therapy, zoledronic acid showed significant efficacy over placebo with regard to the proportion of patients experiencing a skeletal related event (SRE) and the time to the first SRE. It was as effective and as well tolerated as pamidronate 90mg in patients with bone metastases from breast cancer and multiple myeloma. Finally, in patients with lung cancer and other solid tumors, zoledronic acid was statistically significantly better than placebo at delaying the time to the first SRE. In addition, zoledronic acid has a shorter intravenous administration time and a prolonged response time compared to other available bisphosphonates. [3] Zoledronic acid is under investigation for Paget's disease and for direct and anti-tumor effects in breast and prostate cancer cells. The FDA approved zoledronic acid for the treatment of hypercalcemia of malignancy in August 2001.

Table 1: FDA-Approved Indications for Pamidronate and Zoledronic Acid: [1,2]

Indications	Pamidronate	Zoledronic Acid
Paget's Disease	X	
Treatment of hypercalcemia of malignancy	X	X
Osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma	X	
Osteolytic or osteoblastic bone metastases in multiple myeloma and solid tumors in conjunction with antineoplastic therapy; prostate cancer should have progressed after at least one hormonal therapy		X

MECHANISM OF ACTION:

Zoledronic acid inhibits bone resorption by altering osteoclast activity and by inhibiting normal endogenous, as well as tumor induced, mediators of bone degradation. Like other bisphosphonates, zoledronic acid binds to hydroxyapatite crystals in mineralized bone matrix. The binding to calcium phosphates slows the dissolution of hydroxyapatite crystals, as well as inhibiting the formation and aggregation of these crystals. [3]

Zoledronic acid is incorporated into osteoclastic bone surfaces, where it inhibits bone resorption by inhibiting osteoclastic activity and inducing osteoclastic apoptosis. The presence of bisphosphonates in the bone structure appears to prevent acid extrusion, an important step stimulated by osteoclasts during the bone resorption process. Following subsequent resorption, bone tissue surrounding the bisphophonate containing bone tends to lack ruffled borders and has fewer vacuoles, which are changes consistent with lower resorptive capacity. Therefore, osteoclasts may be inhibited not only when bisphosphonates are directly incorporated into the bone matrix, but after they engulf bisphosphonate-containing mineral during active bone resorption, as well. [4,5]

Zoledronic acid affects chemical and hormonal mediators of bone degradation. The exact molecular and biochemical changes leading to osteoclast activity suppression remain unidentified, but are postulated to include reduced production of lactic acid, lysosomal enzymes, pyrophosphatases, and prostaglandins. Bisphosphonates also appear to reduce parathyroid hormone induced bone resorption, where osteoblasts are involved in regulating osteoclast activity.[5]

Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. This may be due to the mediation of release of interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF) by monocytes. These cytokines are involved in osteoclast recruitment and activation.[5]

Zoledronic acid appears to have direct anti-tumor effects in specific types of cancer cells. Zoledronic acid has been demonstrated to inhibit cell growth and induce apoptosis in human myeloma, breast cancer, and prostate cancer cell lines. When studied in breast cancer cell lines, zoledronic acid has been noted to cause dose- and time-dependent reductions in cell numbers and concomitant increases in tumor cell apoptosis. These changes were seen *in vitro* when zoledronic acid was used alone or in combination with paclitaxel and tamoxifen. Although the exact mechanism is unknown, zoledronic acid may mediate this anti-tumor effect by inhibiting the mevalonate pathway. Zoledronic acid has been found to exert effects on certain prostate cancer cell lines, as well. There is no evidence of zoledronic acid inducing prostate cancer cell death, although the drug does appear to inhibit cell proliferation. The exact mechanism of this inhibition is unknown.[6,7]

PHARMACOKINETICS:

Zoledronic acid is administered by intravenous infusion. Zoledronic acid distributes primarily to the bone in a triphasic process. Zoledronic acid plasma concentrations are dose proportional. The elimination is triphasic, with an alpha early distribution half-life of 0.23 hours, a beta half-life of 1.75 hours, and terminal elimination half-life of 167 hours, with low plasma concentrations observed up to 28 days post dose.[1] A complete response, when treating hypercalcemia of malignancy, to a single dose of zoledronic acid is typically seen within 4 to 10 days, lasting up to 3-4 weeks. Plasma protein binding is approximately 22% and independent of zoledronic acid concentrations. Zoledronic acid does not inhibit P450 enzymes in vitro. A study of 32 patients with cancer and bone metastases found that 18% of the administered dose was recovered unchanged in the urine within 24 hours.[15] The remaining drug, representing drug presumably bound to bone, is slowly released back into systemic circulation, giving rise to the prolonged terminal half-life. Clearance correlates with renal function. Clearance does not appear to be influenced by gender, age, or race (Caucasian, African American, or Asian). Limited clinical data are available regarding use of zoledronic acid in patients with renal impairment. Zoledronic acid is excreted primarily via the kidney and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Studies of zoledronic acid in the treatment of hypercalcemia of malignancy excluded patients with serum creatinine ≥ to 4.5 mg/dL.[1] No clinical or pharmacokinetics data are available to guide dose selection or to provide guidance on how to safely use zoledronic acid in patient with severe renal impairment.

Table 2: Comparison of the Pharmacokinetics of Pamidronate and Zoledronic Acid:[1,2]

Pharmacokinetic Parameter	**Pamidronate**	**Zoledronic Acid**
Half-life	28 hours	167 hours
Clearance	107 mL/min	93 mL/min
Renal elimination	Extensive	Extensive

FDA APPROVED INDICATIONS:

Zoledronic acid is indicated for the treatment of hypercalcemia of malignancy and for treatment of bone metastases in patients with multiple myeloma and solid tumors in conjunction with antineoplastic therapy. Patients with prostate cancer should have progressed after therapy with at least one hormonal agent.

CURRENT NATIONAL FORMULARY STATUS:

Non-Formulary

FORMULARY ALTERNATIVES:

Pamidronate for injection: 30 mg/vial and 90mg/vial (Open Formulary)

DOSE ADMINISTRATION:

For the treatment of hypercalcemia of malignancy:

Adults: 4 mg IV over a minimum of 15 minutes. Patients should be adequately hydrated before administration of zoledronic acid. Re-treatment may be considered if serum calcium does not return to normal after seven days. If patients with a normal serum creatinine before treatment have an increase of 0.5 mg/dL or if patients with a serum creatinine prior to treatment have an increase of 1 mg/dL from baseline within two weeks of their next dose, zoledronic acid should be withheld until the serum creatinine is within 10% of baseline.

Zometa is reconstituted by adding 5mL of sterile water for injection to each vial. The recommended 4 mg dose must be further diluted in 100 mL of sterile 0.9% sodium chloride or D5W. The dose must be given as a single intravenous infusion over no less than 15 minutes. If not used immediately after reconstitution, for microbiological integrity, the solution in the vial should be refrigerated at 2 to 8 degrees C (36-46 degrees F). The total time between reconstitution, dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

Table 4: Comparison of Dosing Associated with Pamidronate and Zoledronic Acid Therapy for the Treatment of Hypercalcemia of Malignancy: [1,2]

	Pamidronate	**Zoledronic Acid**
Initial Dose (maximum)	90 mg	4 mg
Time between doses	Minimum of 7 days	Minimum of 7 days
Route of Administration	IV	IV
Rate of administration	≥ 4 hour infusion for 60 mg dose and ≥ 2 hours for 90 mg dose (2-24 hours)	> 15 minute infusion
Hydration therapy	Rehydration prior to and during therapy	Rehydration prior to and during therapy

For the reduction of skeletal-related events in patients with metastases due to solid tumors, multiple myeloma, or prostate cancer:

Adults: 4 mg IV over 15 minutes every 3-4 weeks for up to 6 years has been studied.

For the treatment of active Paget's disease: [9]

A single dose of 200 µg or 400 µg IV has been suggested by the available studies. In a dose-ranging study, patients received a single dose of 24, 72, 216 or 400 µg IV over 1 hour. The 24- and 72-µg doses showed no consistent or meaningful changes in bone resorption markers. The 216 µg dose showed a decrease in urinary hydroxyproline/creatinine (OHP) excretion by a mean of 16-19% on days 3, 7, 10 and 14. The 400 µg dose decreased OHP by mean of 33-48% on days 1, 7, and 10 and by 16% on day 14. Urinary calcium/creatinine decreased from baseline with the 216 µg dose by a mean of 15-40%; the same value decreased with the 400 µg dose by a mean of 55-71%. In a separate controlled study, patients received 200 or 400 µg IV as a single dose. Both treatment groups showed a decrease in urine levels of type II collagen C-telopeptide (a marker for type II collagen destruction) by a median of 25% at 5 days post-treatment; this marker increased to pretreatment levels after 10 days. In contrast, both groups showed a decrease in urine levels of type I collagen C-telopeptide (a marker for bone resorption) within five days with a maximal decrease of 51% at ten days, and levels remained suppressed during the two months of the study.

ADVERSE EFFECTS:

Adverse effects have included bone pain, nausea, constipation, fatigue, confusion, hallucination, anemia, muscle pain, vomiting, weakness, anorexia, fever, dyspnea, eye irritation, hypocalcemia, headache, diarrhea, and hypophosphatemia.[8,9,10,11,12,13]

Adverse effects with zoledronic acid for injection during clinical trials were reported as usually mild and transient. Administration is most commonly associated with fever (44.2%). Occasionally, patients experience a flu-like syndrome consisting of fever, chills, bone pain and/or arthralgias (10%), and myalgia. Gastrointestinal reactions such as nausea/vomiting (29% / 14%) and anorexia (9%) have been reported following administration. Injection site reactions, such as erythema, redness or swelling, were observed infrequently and resolved in most cases without treatment within 24-48 hours.[1]

Azotemia (2%) has been reported during therapy with zoledronic acid; serum creatinine should be monitored. In clinical trials, the incidence of renal failure (unspecified) was significantly increased in patients who received zoledronic acid over 5 versus 15 minutes or who had received doses of 8 mg versus 4 mg over 15 minutes.

Electrolyte imbalances may occur during treatment with zoledronic acid. Hypocalcemia (1.2%), hypomagnesemia (10%), and hypophosphatemia (52%) have been reported. Monitor serum calcium, phosphate, and magnesium during therapy; short-term supplementation of these electrolytes may be necessary.[1]

Rare cases of rash (unspecified), pruritus, and chest pain (unspecified) have been reported. Bronchospasm has not been reported in any patients receiving zoledronic acid; however, bronchospasm due to phosphonate sensitivity or aspirin-sensitive asthma has been associated with other bisphosphonates, and therefore, have the potential to occur with zoledronic acid. As with other bisphosphonates, cases of conjunctivitis have been reported following treatment with zoledronic acid.[1]

Other adverse events that have been reported in >1% of patients in the zoledronic acid treatment group, compared to the control group, in clinical trials include abdominal pain, agitation, anemia, anxiety, confusion, constipation, cough, diarrhea, dyspnea, hypotension, insomnia, candidiasis, and urinary tract infection.[1]

Table 3: Most Common Adverse Effects Associated with the Use of zoledronic Acid and Pamidronate in Patients Treated for Hypercalcemia of Malignancy:[11,15]

Adverse Events	Zoledronic Acid 4 mg (n=86)	Pamidronate 90 mg (n=103)
Fever	44.2%	33%
Nausea	29.1%	27.2%
Constipation	26.7%	12.6%
Anemia	22.1%	17.5%
Dyspnea	22.1%	19.4%
Diarrhea	17.4%	16.5%
Abdominal pain	16.3%	12.6%
Progression of cancer	16.3%	20.4%
Insomnia	15.1%	9.7%
Anxiety	14%	7.8%
UTI	14%	14.6%
Vomiting	14%	16.5%
Agitation	12.8%	7.8%
Confusion	12.8%	12.6%
Hypophosphatemia	12.8%	1.9%
Coughing	11.6%	11.7%
Hypokalemia	11.6%	15.5%
Hypomagnesemia	10.5%	4.9%
Hypotension	10.5%	1.9%

Note: the differences in tolerance are not clinical significant.

WARNING/CONTRAINDICATIONS: [1]

The contraindications, warnings, and precautions for zoledronic acid are expected to be similar to those of pamidronate.

Zoledronic acid is contraindicated in patients with clinical hypersensitivity to zoledronic acid monohydrate or other bisphosphonates, or any of the excipients in the injectable formulation (mannitol, sodium citrate).

In clinical trials, the risk of renal function deterioration was increased in patients who received zoledronic acid over 5 minutes compared to patients who received the same dose over 15 minutes. The risk of renal function deterioration and renal failure was also increased in patients receiving 8 mg dose, even when it was administered over 15 minutes.

Due to risk of renal toxicity, including renal failure, avoid intravenous administration over less than 15 minutes or doses greater than 4 mg. Monitor renal function prior to and during treatment, especially in patients with preexisting renal impairment. Re-treatment should be delayed in patients who develop increased serum creatinine following the initial dose. Risk of zoledronic acid treatment must be carefully considered in patients with renal failure or impairment. Caution is recommended when zoledronic acid is administered to elderly patients due to the greater frequency of decreased renal function and concomitant disease states or other drug therapy.

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored during treatment with zoledronic acid. Zoledronic acid should not be used in patients with pre-existing hypocalcemia. If electrolyte imbalance (i.e., hypocalcemia, hypomagnesemia, or hypophosphatemia) occurs during therapy, short-term supplementation may be necessary.

Dehydration or hypovolemia should be corrected during treatment of hypercalcemia and prior to beginning zoledronic acid therapy; maintain urine output of 2L/day during treatment of hypercalcemia.

While not observed with zoledronic acid, treatment with bisphosphonates has been associated with acute bronchospasm in patients with aspirin-sensitive asthma and phosphonate hypersensitivity.

Zoledronic acid is classified as FDA pregnancy risk category C. In animal studies, administration of zoledronic acid was associated with increased pre- and post-implantation losses and stillbirths; decreased neonatal survival; skeletal, visceral, and external malformations; and adverse maternal effects including periparturient mortality. Because no adequate and well-controlled studies of zoledronic acid have been conducted in pregnant women, the drug should be avoided during pregnancy whenever possible.

DRUG INTERACTIONS:

Loop diuretics should be used with caution in combination with zoledronic acid in order to avoid hypocalcemia. The initial treatment of hypercalcemia typically includes the use of loop diuretics, in combination with saline hydration; however, diuretic therapy should not be employed prior to correction of hypovolemia and dehydration.

Caution is recommended when bisphosphonates are administered with aminoglycosides since these agents may have an additive effect to lower serum calcium levels for prolonged period.

CLINICAL EFFICACY: (Please see appendix for clinical trials)

Hypercalcemia of Malignancy

A pooled analysis was performed on two identical, concurrent, double-blind trials comparing zoledronic acid and pamidronate in the treatment of hypercalcemia of malignancy. Patients with moderate-to-severe hypercalcemia were treated with single dose of zoledronic acid 4 mg or 8 mg as an infusion over 5 minutes or pamidronate 90 mg as an infusion over 2 hours. Patients were followed for 56 days or until relapse (corrected serum calcium > or equal to 2.9 mmol or 11.6 mg/dL). Safety was assessed in 287 patients (total number of patients were 287), efficacy in 275. A complete response by day-10 was achieved in 88.4% of patients treated with zoledronic acid 4 mg (p=0.002), 86.7% treated with zoledronic acid 8 mg (p=0.015), and 67.9% treated with pamidronate. Normalization of corrected serum calcium by day-4 occurred in 55.6% of patients treated with zoledronic acid 8 mg and 33.3% of patients treated with pamidronate (p=0.021). Zoledronic acid 4 mg was associated with normalization of corrected serum calcium by day-4 in 45.3% of patients. The median duration of complete response was 32 days with zoledronic acid 4 mg, 43 days with zoledronic acid 8 mg, and 18 days with pamidronate. [11,13]

Zoledronic acid was also evaluated in a dose-finding study enrolling 33 patients with hypercalcemia of malignancy. Doses administered were 0.002 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.02 mg/kg, and 0.04 mg/kg. Median infusion time was 3.0 minutes. The mean baseline calcium level was 3 mmol/L. Calcium levels normalized in 5 of 5 patients treated with zoledronic acid 0.02 mg/kg and 14 of 15 patients treated with zoledronic acid 0.04 mg/kg. At the highest dose, calcium levels normalized within 2 to 3 days of administration.[10]

Metastatic Bone Lesions

Zoledronic acid was compared with pamidronate in a double-blind study enrolling 280 patients with osteolytic metastatic lesions due to breast cancer or multiple myeloma. Patients received zoledronic acid 0.4 mg, 2 mg, or 4 mg as a 5-minute infusion, or pamidronate 90 mg as a 2-hour infusion. Doses were repeated every 4 weeks for up to 10 months. The need for radiation therapy to bone was reduced with zoledronic acid 2 mg and 4 mg and with pamidronate 90 mg ($p<0.05$), but not with the lower zoledronic acid dose. Skeletal-related events, pathologic fractures, and hypercalcemia occurred less frequently among patients treated with zoledronic acid 2 mg or 4 mg or pamidronate, than among patients treated with the lower zoledronic acid dose.[15]

Three studies were presented to the Oncologic Drugs Advisory Committee for approval in the treatment of bone metastases. The first study presented to the FDA (#010) was a trial of zoledronic acid 4mg and 8mg versus pamidronate 90mg in 1648 patients with either multiple myeloma or breast cancer. The infusion time of zoledronic acid was increased to 15 minutes with 100ml of diluent, the 8mg arm was dropped and patients were converted to 4mg because of renal failure in the 8 mg arm. The pamidronate was given over 2 hours. The primary objective was the proportion of patients experiencing at least one skeletal related event (SRE). Secondary endpoints included time to first SRE, pain scores, analgesic scores, QoL, biochemical variables, safety and tolerability. SRE's included pathologic bone fractures, spinal cord compression, surgery to bone for stabilization, radiation therapy to bone, and change in antineoplastic therapy to treat bone pain. It excluded hypercalcemia of malignancy. Because this was a comparison to active treatment, it was designed as a non-inferiority trial. Zoledronic acid was shown to be as effective as pamidronate in decreasing skeletal morbidity, primarily the proportion of patients with any SRE and the time to first SRE.[14]

Zoledronic acid was compared in a double-blind, placebo controlled randomized trial (#039) of safety and efficacy in 643 prostate cancer patients with bone metastases despite first line hormonal therapy. Patients were randomized to zoledronic acid 4mg or 8 mg or placebo given IV every 3 weeks. Primary and secondary endpoints were similar to the breast cancer and multiple myeloma study. Concerns about safety (renal failure) prompted amendments to drop the 8mg arm and change everyone to 4mg as well as increasing the diluent and infusion time. The percent of patients experiencing at least one SRE was statistically significantly less in the 4mg arm versus placebo, but was not significant in the 8/4mg arm. Similarly, the median time to the first SRE has not been reached in the 4mg arm but was similar in the 8/4mg and placebo arms (follow-up of 15 months). The final study compared zoledronic acid 4mg and 8mg to placebo in a double blind randomized trial (#011) in 766 patients with any cancer with bone metastases other than breast cancer, prostate cancer, or multiple myeloma. Primary and secondary endpoints were similar to the prostate cancer study. The same concerns with renal failure and the 8 mg dose prompted amendments to change all on the 8mg dose to 4mg and increase the diluent volume and infusion time. There was a statistically significant difference in the percent of patients with at lease 1 SRE in the 8mg/4mg group versus placebo but not in the 4mg group versus placebo. The time to first SRE (more sensitive than the proportion of patients with SRE because it takes into account the timing of dropouts [primarily due to death]) in the 4mg group was 67 days longer than in the placebo group ($p= 0.026$) and 56 days longer in the 8mg/4mg group ($p=0.035$). An analysis of stratification groups shows some disadvantage for non small-cell lung cancer versus other solid tumors.[15]

Several large studies have also been proposed to assess the efficacy and tolerability of zoledronic acid in conjunction with standard adjuvant therapy in the prevention of disease recurrence in patients with node-positive breast cancer, prevention of bone metastases in breast cancer, and the prevention of bone metastases in prostate cancer.[16]

Paget's Disease

Zoledronic acid was evaluated in a double-blind, placebo-controlled, dose-ranging study enrolling 176 patients with Paget's disease of bone. Patients received a single 1-hour infusion of zoledronic acid 50 mcg, 100 mcg, 200 mcg, or 400 mcg, or placebo. Median fasting urinary hydroxyproline and creatinine excretion was reduced in all four zoledronic

acid groups, reaching a nadir by day-10. Reductions occurred sooner at the 200 and 400 mcg doses. Serum alkaline phosphatase activity also dropped, reaching a nadir by day-60 at the 50 mcg, 100 mcg, and 200 mcg doses and continued to drop at day-90 at the 400 mcg dose. All doses were more effective than placebo at day-5. The 400 mcg dose was more effective than the 50 and 100 mcg dose. At the 400 mcg dose, a 50% decline in serum alkaline phosphatase from pretreatment was observed in 46% of patients, and normalization of serum alkaline phosphatase was achieved in 20%.[17]

In another dose-finding study, zoledronic acid was administered to 16 patients with Paget's disease at doses of 24 mcg, 72 mcg, 216 mcg, or 400 mcg as a single 1-hour infusion. Twenty-four hour urinary hydroxyproline/creatinine excretion was reduced by a mean of 16% to 19% from baseline on days 1, 3, 7, 10 and 14 at the 216 mcg dose and by 55% to 71% at the 400 mcg dose. Change in serum alkaline phosphatase was not observed within the 14-day follow-up period.[18]

Osteoporosis

Zoledronic acid was evaluated as a single annual injection in the treatment of postmenopausal osteoporosis in a placebo-controlled study enrolling 351 postmenopausal women with T-score less than –2. Zoledronic acid was administered intravenously at doses of 0.25 mg, 0.5 mg and 1 mg every 3 months, 4 mg as a single dose, and 2 mg every 6 months. After 1 year, mean bone-specific alkaline phosphatase was reduced about 40% from baseline. Changes in mineral density appeared comparable regardless of the dosage regimen.[19]

ACQUISITION COSTS:

Updated April 2002

Drug	Trade Name	Strength	Price
Pamidronate	Aredia	30mg	$161.45
Pamidronate	Aredia	90mg	$433.07
Pamidronate	(Bedford generic)	30mg	$150.00
Pamidronate	(Bedford generic)	90mg	$410.00
Zoledronic acid	Zometa	4mg	$521.69

VHA Purchasing Information

Pamidronate 90mg/vial (4/4/01 – 3/31/02)

VISN	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
# of vials	386	338	313	431	431	343	325	255	383	171	179	703	388	163	189	598	458	51	374	383	436	432

Zoledronic Acid 4mg/vial (9/1/01 – 3/31/02)

VISN	1	2	3	5	6	8	9	13	14	15	17	18	19	21	22
# of vials	10	7	24	42	101	39	15	4	10	14	10	14	7	1	2

CONCLUSION:

Zoledronic acid appears to be a potent bisphosphonate with promising activity in the treatment of hypercalcemia of malignancy.

Results from the treatment of bone metastases show it has equivalent clinical efficacy versus pamidronate in breast cancer and multiple myeloma and provides a clinical benefit in a reduced incidence of radiation therapy to the bone. Unlike pamidronate, zoledronic acid has significant activity versus placebo in osteoblastic lesions in prostate cancer. In patients with other solid tumors and bone metastases, the 4 mg doses did not show a statistically significant decrease in the proportion of patients with at least one SRE versus placebo although the 8mg/4mg group did produce a

significant decrease; both the 4mg and the 8mg/4mg significantly increased the time to the first SRE in a population whose life expectancy is relatively short. This increase in time to first SRE may translate into delay in additional treatment of bone metastases in this particular group (e.g. radiation therapy), although this benefit was not evident in non small-cell lung cancer when the stratification groups were sub-analyzed. The addition of a new indication in patients with prostate cancer metastatic to the bone will add new patients not currently using bisphosphonate therapy. A review of the tumor registry for the years 1992, 1998, and 1999 (the most current data available) reveals that the number of metastatic prostate cancer cases reported in the VHA was 764, 925, and 641, respectively. The data on patients with other solid tumors is difficult to interpret. While the increased time to SRE could translate into clinical benefit (e.g. decreased time spent in clinic for those with a short life expectancy), it is unclear which sub-populations will benefit most.

In addition, in other areas like Paget's disease and osteoporosis, zoledronic acid is showing some data comparable to pamidronate. Unless additional adverse effects become evident, zoledronic acid is likely to replace pamidronate as first-line therapy in hypercalcemia of malignancy due to its increased efficacy and shorter infusion time.

RECOMMENDATION:

Patients with hypercalcemia of malignancy do not receive scheduled infusions of bisphosphonates. Therapy is initiated based on laboratory results as well as signs and symptoms of disease. In addition, within this subset of patients, the majority receives their dose of bisphosphonate (currently pamidronate) during an inpatient admission. In those cases, the cost saving due to shorter infusion time does not apply.

In contrast, the majority of patients with bone metastases receive their dose of bisphosphonate on a scheduled basis (every 3 or 4 weeks) over a prolonged period of time (months to years) primarily in the outpatient setting. A shorter infusion time would mean patients would spend less time in the outpatient center, and chairs or stations in the outpatient setting would turn over at a quicker rate. This might translate into cost savings of personnel resources and provide a quality of life benefit to patients. The recommendation is not to add zoledronic acid to the national formulary, but allow individual VISNs to add the drug to their VISN formularies. Use should be restricted to patients with bone metastases from breast cancer, multiple myeloma, or prostate cancer. Use in patients with other solid tumors and bone metastases may be considered.

REFERENCES:

1) Novartis Pharmaceutical Corporation. Package literature for Zometa. February 2002.
2) Novartis Pharmaceutical Corporation. Package literature for Aredia. April 2000.
3) Green JR. Chemical and biological prerequisites for novel bisphosphonate molecules: Results of comparative preclinical studies. Semin Oncol 2001; 28(Supp 6):4-10.
4) Green J. Zoledronate: The preclinical pharmacology. Br J Clin Pract Symp Suppl 1996;87:16-8.
5) Lourwood DL. The pharmacology and therapeutic utility of bisphosphonates. Pharmacotherapy 1998;18:779-89.
6) Jagdev SP, Coleman RE, Shipman CM et al. The bisphosphonate, zoledronic acid, induces apoptosis of breast cancer cells: evidence for synergy with paclitazel. Br J Cancer 2001;84:1126-34.
7) Lee MV, Fong EM, Singer FR et al. Bisphosphonate treatment inhibits growth of prostate cancer cells. Cancer Res 2001;61:2602-8.
8) Arden-Cordone M, Siris ES, Lyles KW et al. Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. Calcif Tissue Int 1997;60:415-8.
9) Garnero P, Christgau S, Delmas PD. The bisphosphonate zoledronate decreases type II collagen breakdown in patients with Paget's disease of bone. Bone 2001;28:461-4.
10) Body JJ. A dose-finding study of zoledronate in hypercalcemic cancer patients. J Bone Miner Res 1999;14:1557-61.
11) Major P. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19:558-67.
12) Mundy GR. Preclinical studies with zoledronic acid and other bisphosphonates: Impact on the bone microenvironment. Semin Oncol 2001;28(Suppl 6):35-44.

13) Major PP, Coleman RE. Zoledronic acid in the treatment of hypercalcemia of malignancy: Results of the international clinical development program. Semin Oncol 2001;28(Suppl 6):17-24.
14) Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Zoledronic Acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase II, double-blind, comparative trial. Cancer J 2001;7(5):377-387.
15) FDA clinical briefing document for the Oncologic drugs advisory committee. Zometa (zoledronic acid for injection). Center for Drug Evaluation and Research. http://www.fda.gov/ohrms/dockets/ac/02/briefing/3827b1_03_FDA Part1.pdf
16) Coleman Re, Seaman JJ. The role of zoledronic acid in cancer: Clinical studies in the treatment and prevention of bone metastases. Semin Oncol 2001;28(Suppl 6):11-16.
17) Berenson JR, Rosen LS, Howell A et al. Zoledronic acid reduces skeletal related events in patients with osteolytic metastases: a double-blind, randomized dose-response study. Cancer. 2001;91(7):1191-1200.
18) Buckler H. Single infusion of zoledronate in Paget's Disease of bone: A placebo-controlled, dose ranging study. Bone 1999;24:81S-85S.
19) Reid IR. A single annual injection of the bisphosphonate, zoledronic acid, stably reduces bone turnover and increases bone density in postmenopausal osteoporosis [abstract]. Bone 2001;28(5, Suppl):S89.

PREPARED BY: Cindy Lee, Pharm D
Pharmacy Resident

REVIEWED BY: Brendan McDonald, RPh
Clinical Pharmacist, MTU

William Schubach, MD
Chief, Oncology Section

VA Puget Sound

Updated By: Mark C. Geraci, Pharm.D.
Medical Advisory Panel
VA Oncology Field Advisory Committee
May 2002

APPENDIX: REVIEW OF CLINICAL TRIALS

Citation	Major P. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001 Jan 15;19:558-67.
Objective	To determine the efficacy and safety of 2 doses of zoledronic acid compared with pamidronate, which was the current standard of care for the treatment of moderate to severe hypercalcemia of malignancy.
Methods	Two parallel, multicenter, randomized, double-blind, double-dummy trials were conducted in the United States/Canada and Europe/Australia. Inclusion criteria: Patients ≥ 18 years of age With histologic or cytologic confirmation of cancer hypercalcemia of malignancy, defined as baseline corrected serum calcium ≥ 12.0 mg/dL. Exclusion criteria: History of allergic reaction or sensitivity to bisphosphonates

	Bisphosphonate treatment for HCM within 90 days or for other Complications within 30 days of study entry Serum creatinine > 4.5 mg/dL Treatment with calcitonin within 72 hours Mithramycin or with a newly initiated antineoplastic cytotoxic chemotherapy Hormone therapy within 7 days of study entry Gallium nitrate within 14 days of study entry Investigational drug within 30 days of study entry Severely dehydrated, could not tolerate IV, hyperparathyroidism, adrenal insufficiency, vitamin D intoxication, milk alkali syndrome, sarcoidosis or other granulomatous disease, or multiple endocrine neoplasia syndromes Patients enrolled in these studies were randomized to 4 mg of Zoledronic acid, 8 mg of Zoledronic acid, or 90 mg of Pamidronate. The 3 treatment arms consisted of a single dose of Zoledronic acid (4 mg or 8 mg) via 5-minute infusion or Pamidronate (90 mg) via 2-hour infusion. In addition, all patients received a double dummy infusion, to maintain the double-blind nature of the trial. The primary objective was to assess the ability of the 2 doses of zoledronic acid as therapy for HCM to achieve complete response rates defined as normalization of corrected serum calcium. Secondary objectives include time to relapse; duration of response, duration of complete response, and the efficacy of zoledronic acid re-treatment for relapsed or refractory HCM. The safety and tolerability of zoledronic acid were also assessed. Patients refractory to or relapsing within 56 days of initial treatment were eligible for re-treatment with 8 mg of Zoledronic acid.
Results	A total of 287 patients were enrolled in the combined trials and evaluated for safety. Of these, 275 patients were evaluable for efficacy: 86 patients in the 4 mg Zoledronic acid dose group; 90 patients in 8 mg Zoledronic acid dose group; and 99 patients in the 90 mg Pamidronate dose group. Both doses of Zoledronic acid were statistically significantly more effective than Pamidronate in normalizing corrected serum calcium ($P < 0.001$); 88.4% and 86.7% of patients treated with 4 mg or 8 mg Zoledronic acid, respectively, achieved a complete response compared with 69.7% of patients treated with 90 mg Pamidronate by Day 10. Furthermore, Zoledronic acid-treated patients achieved normocalcemia significantly faster and exhibited a significantly longer time to relapse than patients treated with Pamidronate. The median time to relapse and median duration of complete response were significantly longer in both Zoledronic acid dose groups compared with the Pamidronate group. Zoledronic acid 4 mg Zoledronic acid 8 mg Pamidronate 90 mg

	Median duration of complete response (days) 32 43 18 Median time to relapse (days) 30 (p=0.001) 40 (p=0.007) 17 All 287 patients originally randomized were evaluated for safety parameters. Zoledronic acid was safe and well tolerated at both dose levels and demonstrated a safety profile similar to Pamidronate 90 mg.
Conclusions	Zoledronic acid is superior to pamidronate. With the similar SE profile, zoledronic acid has shown to be faster onset, longer acting, and more potent. The 4 mg zoledronic acid is the dose recommended for initial treatment of HCM, the 8mg of zoledronic acid is for relapsed or refractory hypercalcemia.

Citation	Berenson JR, Rosen LS, Howell A et al. Zoledronic acid reduces skeletal related events in patients with osteolytic metastases: a double-blind, randomized soe-response study. Cancer. 2001;91(7):1191-1200.
Objective	To evaluate the dose-response relation for zoledronic acid for patients with malignant osteolytic disease.
Methods	In a phase II double-blind, randomized comparative study of pamidronate and zoledronic acid. A total of 280 patients (172 with breast cancer and 108 with multiple myeloma) with osteolytic lesions received monthly infusions of either 0.4 mg , 2 mg or 4 mg of zoledronic acid or 90 mg of pamidronate. Inclusion criteria: Patients with multiple myeloma were required to have had a previous skeletal event (radiation to bone, pathological fracture, surgery to bone, spinal cord compression or hypercalcemia). All patients had to have a life expectancy of at least 10 months and an ECOG performance status of 0, 1, or 2. Exclusion criteria: Osteolytic lesions only in previous radiated areas, prior bisphosphonate treatment, or a recent history of hypercalcemia or bisphosphonate allergy or sensitivity. The treatments were given every 4 weeks for up to 10 months. The dose of zoledronic was administered as a 5-minute IV infusion and the pamidronate as a 2-hour IV infusion. The primary efficacy variable was the proportion of patients having radiation to bone within the 10 month observation period. A treatment arm was considered successful if there was need for radiation therapy to bone to significantly less than 30% of the patients within the group. Such significance was exhibited in the 2 and 4 mg of zoledronic acid groups, as well as the pamidronate group. Secondary efficacy variables included the number and type of skeletal-related events, bone mineral density, ECOG performance status, pain score, and

	analgesic score. There was a trend to decreasing skeletal events (fractures, radiation therapy to bone, orthopedic surgery, hypercalcemia, or spinal cord compression) for doses greater than 0.4 mg of zoledronic acid and pamidronate (46%, 35%, 33%, 30% for the 0.4 mg zoledronic acid, 2mg zoledronic acid, 4 mg zoledronic acid and 90 mg pamidronate groups, respectively).
Results	Increases in both bone mineral density and inhibition of bone resorption markers were noted in all groups at the end of the 10-month study. While there was improvement in the ECOG scores in a greater percentage of patients who had an ECOG performance > 0 at entry in the 2 mg and 4 mg of zoledronic groups (28% and 24%, respectively) than in the 0.4 mg of zoledronic acid and 90 mg of pamidronate (8% and 13%, respectively), this trend was not statistically significant. The safety profile for zoledronic acid was similar to that of pamidronate.
Conclusions	Zoledronic acid in low doses, given over 5 minutes provides comparable results to 90 mg pamidronate in patients with osteolytic disease.

Citation	Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Zoledronic Acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase II, double-blind, comparative trial. Cancer J 2001;7(5):377-387.
Objective	To evaluate the efficacy and safety of 4mg and 8mg of zoledronic acid with 90mg of pamidronate in breast cancer patients with osteolytic or mixed bone metastases and patients with multiple myeloma with osteolytic bone lesions.
Methods	A phase II multicenter, randomized, double-blind, double-dummy, parallel group study of pamidronate and two different doses of zoledronic acid. A total of 1648 patients (1,130 breast and 513 multiple myeloma) received either zoledronic acid 4mg, 8mg, or pamidronate 90mg iv infusion every 3-4 weeks. Inclusion criteria: Adult patients with stage III multiple myeloma and lytic bone lesions or breast cancer with lytic or mixed lesions that are receiving chemotherapy. Breast cancer patients could receive hormonal therapy only if it was as first or second line treatment unless it was in conjunction with chemotherapy. Antineoplastic therapy could be changed or discontinued as needed. An ECOG performance status of 2 or less was required. Exclusion criteria: Receipt of a bisphosphonate in the last 12 months, hypercalcemia (corrected calcium ≥12mg/dl), serum creatinine level >3mg/dl, bilirubin /2.5mg/dl, pregnancy, lactation, or history of noncompliance. Zoledronic acid was given as a 5-minute infusion every 3-4 weeks (to coincide with antineoplastic therapy). Because of concerns with renal failure, the diluent was increased to 100ml and the infusion time was increased to 15 minutes. A second amendment to the protocol required patients originally assigned to the 8 mg are to receive 4 mg instead; the 8mg arm was dropped from the study. The pamidronate 90mg was given over 2 hours. Treatment was continued for 12 months. All patients received 400-500 international units of vitamin D and a daily 500mg calcium supplement.

	Primary efficacy endpoint was the proportion of patients who had at least one skeletal related event (SRE) excluding hypercalcemia of malignancy. Secondary endpoints included the proportion of patients experiencing any SRE (including hypercalcemia), the time to the first SRE, skeletal morbidity rate, proportion of patients with individual SREs, time to progression of one metastasis, objective bone lesion response, time to overall progression of disease, ECOG performance status, analgesic and pain scores, and bone resorption and formation markers.

Results

Patient Characteristics

	Zol 4mg (n = 563)	Zol 8/4mg (n = 524)	Pamidronate (n = 556)	Total (n = 1,643)
Gender (%)				
Male	104 (18)	96 (18)	92 (17)	292 (18)
Female	459 (82)	428 (82)	464 (83)	1,351 (82)
Median age, Years	60	59	58.5	
Type of cancer				
Breast	377 (67)	364 (69)	389 (70)	1130 (69)
Multiple Myeloma	186 (33)	160 (31)	167 (30)	513 (31)
Time since Diagnosis, months	58.7 ± 64.6	59 ± 70.4	55.6 ± 60.9	
ECOG status				
0-1	476 (85)	429 (82)	437 (79)	1,342 (82)
≥ 2	86 (15)	94 (18)	116 (21)	296 (18)
BPI composite Pain score	3.9 ± 2.1	3.2 ± 2.3	3.0 ± 2.2	
Previous SRE				
No	181 (32)	187 (36)	176 (32)	544 (33)
Yes	382 (68)	337 (64)	380 (68)	1,099 (67)
Baseline Serum Cr				
Normal (<1.4)	511 (91)	475 (91)	514 (92)	1,500 (91)
Abnormal (≥1.4)	47 (8)	43 (8)	37 (7)	127 (8)

Efficacy Results – Primary Endpoint

Proportion of Patients with At least 1 SRE at Month 13	No. of Patients (%)		
	Zol 4mg	Zol 8/4mg	Pamidronate
Multiple Myeloma	86/183 (47)	79/160 (49)	82/167 (49)
Breast Cancer on chemotherapy	79/178 (44)	80/172 (47)	78/181 (43)
Breast Cancer on Hormonal Tx	83/200 (42)	83/192 (43)	97/201 (47)
Total	248/561 (44)	242/524 (46)	257/555 (46)

Secondary Endpoints

- Median Time to First SRE
  Zoledronic Acid 373 days
  Pamidronate 363 days NSS
- BPI Composite Scores decreased in all groups
- ECOG performance status was stable in multiple myeloma patients but worsened for breast cancer patients by the study's end
- Bone Lesion Response
  Partial response in 17 and 18%, no response in 30% and 28% of zoledronic acid 4mg and pamidronate groups, respectively
- Bone Markers
  All markers decreased from baseline. N-telopeptide decreased by 64 % in

zoledronic acid 4mg group versus 57% in the pamidronate group (P= 0.015)

- Skeletal Morbidity Rate (events/yr) by Treatment Group (Intent-to-Treat)

	Zoledronic Acid (4mg) (N=561)	Zoledronic Acid (8/4mg) (N=524)	Pamidronate 90mg (N=555)
All SREs	1.13	1.08	1.40
Pathologic Fractures	0.62	0.61	0.66
Vertebral Fractures	0.27	0.27	0.27
Nonvertebral Fractures	0.41	0.40	0.45
Spinal Cord Compression	0.03	0.03	0.09
Radiation to bone	0.47*	0.47	0.71
Surgery to bone	0.05	0.04	0.10

*P=0.018 for 4mg zoledronic acid vs pamidronate

Adverse Events Reported in ≥ 15%
The most common adverse events were bone pain, nausea, fatigue, and fever and were similarly reported in all groups. The highest incidence of serious adverse events was reported in the 8/4mg group (4.6%) versus the 4mg (1.8%) and pamidronate (1.4%) groups.

Serious adverse events related to the drug caused 6-7% of patients to stop therapy.

Patients with deterioration of renal function

	No. of Patients (%)		
Baseline Creatinine	Zol 8/4mg	Zol 4mg	Pamidronate
Before Amendment to 15 minute infusion			
Normal	45/223 (20)	30/252 (12)	17/255 (7)
Abnormal	4/17 (24)	6/20 (30)	1/15 (7)
After Amendment to 15 minute infusion			
Normal	43/242 (18)	23/246 (9)	20/246 (8)
Abnormal	6/21 (29)	1/26 (4)	2/22 (9)

Normal baseline creatinine <1.4mg/dL Deterioration defined as change from baseline ≥0.5mg/dl or ≥2 times baseline value.
Abnormal baseline creatinine ≥1.4mg/dL and deterioration defined as a change from baseline ≥1mg/dL or ≥2 times baseline

Conclusions

- Zoledronic acid is clinically equivalent to pamidronate in reducing the incidence of SRE's in patients with breast cancer and multiple myeloma
- Zoledronic acid 4mg provided a statistically significant clinical benefit over pamidronate in the incidence of radiation therapy to bone.
- Zoledronic acid significantly reduced the excretion of N-telopeptide compared to pamidronate
- Renal impairment at a dose of 4mg infused in 100ml over 15 minutes was comparable to pamidronate; higher doses and/or shorter infusion times may be associated with an increased risk for deterioration of renal function.

Critique

- Limitations
  - Designed as a single study non-inferiority trial
  - Primary endpoint is not the one desired by the FDA; time to first SRE is a desired endpoint because it takes into account drop-outs and deaths
  - Assumes data from multiple myeloma and breast cancer can be

	analyzed together ➢ Zoledronic acid 8mg/4mg arm produced highly variable results which were often contradictory of the 4mg arm; no explanation is given for this arm and it was not used to calculate some of the outcomes • Strengths ➢ Randomized, double-blind, double-dummy trial decreases chance of bias in results

Citation	DesHarnais C, Bajwa K, Markle JP et al. A micro-costing analysis of zoledronic acid and pamidronate therapy in patients with metastatic bone disease. Support Care Cancer 2001 Oct;9(7):545-51.
Objective	To calculate resource use associated with administration of zoledronic acid, compared with pamidronate, as palliative care of patients with metastatic bone lesions.
Methods	Time-and-motion study of therapy administration at each of three outpatient chemotherapy infusion sites participating in clinical trials of zoledronic acid and pamidronate. The researcher developed a data-collection instrument to record all staff effort and patient resource use drug administration. The main outcome measures were (a) direct costs of therapy administration per patient and (b) opportunity benefits expressed as availability of resources gained per year.
Results	The opportunity benefit for infusion of zoledronic acid vs pamidronate in the basic case was 1.8 chairs per day, or 426 chairs per 240-workingday year.
Conclusions	The results were sensitive to changes in infusion facility size, days of operation, and average number of patients treated. Shorter infusion time associated with the administration of zoledronic acid, compared with pamidronate, yields substantial time savings for patients, as well as opportunity benefits for outpatient oncology facilities.

ATTACH C (Continued)

DRUG-SPECIFIC CONFLICT OF INTEREST DISCLOSURE FORM

Regarding zoledronic acid (Zometa®), marketed by Novartis Pharmaceuticals: _____
(Name)

I, my spouse, significant other or minor children have received a grant to perform research within the past 5 years for the following pharmaceutical companies. For any grant support for Novartis, please list the project, and grant amount:

_____

_____

_____

I, my spouse, significant other or minor children have received financial remuneration from pharmaceutical manufacturers for performing consulting activities, speakers board presentations, or other activities which could constitute the appearance of a conflict of interest.

[Please list the activity and company(ies) involved].

_____

_____

_____

I, my spouse, significant other or minor children hold stock in a pharmaceutical company.

[Please list the activity and company(ies) involved].

_____

_____

_____

_____ _____
(Signature) (Date)