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# Zoledronic Acid

(Zometa® — Novartis)

## Summary

**Indications:** Zoledronic acid is approved for the treatment of hypercalcemia of malignancy. In addition, it has been studied for postmenopausal osteoporosis, Paget's disease and osteolytic bone metastases.

**Dose:** The recommended dose is 4 mg diluted in 100 mL and infused over no less than 15 minutes. The dose may be repeated as needed at no less than 7-day intervals. In clinical trials repeat doses of zoledronic acid were given at 3 to 4 week intervals in order to coincide with concomitant chemotherapy. Patients should be adequately hydrated prior to treatment with zoledronic acid to reduce the risk of renal toxicity.

**Monitoring Parameters:** Calcium, phosphate, and magnesium levels should be monitored during treatment with zoledronic acid. Serum creatinine should be measured at baseline and periodically thereafter.

**Pregnancy Category:** C. Zoledronic acid was associated with an increased number of stillbirths and a decreased neonatal survival rate in rats receiving doses > 0.2 times the adjusted human dose. At doses 2.4 to 4.8 times the comparable human dose there were increased fetal skeletal, visceral and external defects, including incomplete bone ossification, malformed bones, wavy rib, shortened jaw, reduced lens, rudimentary cerebellum, reduced or absent liver lobes, reduced lung lobes, vessel dilation, cleft palate and edema.

**Breast Feeding:** It is not known if zoledronic acid is excreted in human breast milk.

**Pediatrics:** The safety and efficacy of zoledronic acid in pediatric patients have not been established.

**Geriatrics:** No differences in response rate or adverse effects were noticed based simply on age. However, zoledronic acid should be used with caution in elderly patients due to age-related decline in renal function.

**Cost:** The average acquisition price for zoledronic acid 4-mg is \$744.81 (AWP of \$953.61). In contrast, the average acquisition price for the now generically available pamidronate 90-mg is approximately \$300.

## Introduction

Hypercalcemia of malignancy (HCM) is a common metabolic complication of cancer affecting up to 30% of cancer patients.<sup>1</sup> An imbalance in bone resorption and formation results in increased serum calcium concentrations which in

turn may cause fatigue, anorexia, polyuria, nausea, vomiting, confusion, and even, coma.<sup>2</sup> Approximately 80% of HCM is caused by humeral factors, the rest by local osteolysis. The primary treatments for HCM are rehydration and bisphosphonates, typically pamidronate (Aredia® — Novartis).<sup>3</sup> To reduce the potential for renal toxicity, pamidronate must be infused over a minimum of 2 hours making it inconvenient for both the patient and the providers. Zoledronic acid (Zometa® — Novartis) is a new, potent bisphosphonate that offers a more convenient means of managing HCM.

## Pharmacology

Zoledronic acid is a third-generation bisphosphonate. Analogs of pyrophosphate, the bisphosphonates bind to calcium hydroxyapatite in the skeleton blocking calcium release. They inhibit osteoclast formation and osteoblast proliferation and induce osteoclast apoptosis.<sup>4,5</sup> These agents also block skeletal calcium release induced by various factors released by tumors.<sup>6</sup> Both zoledronic acid and pamidronate have been shown to have direct antitumor effects *in vitro*. Zoledronic acid induces cell apoptosis and inhibits proliferation in human breast, prostate, and myeloma cell lines.<sup>7-10</sup> The clinical significance of this antitumor activity has not been established.

## Pharmacokinetics

Zoledronic acid plasma concentrations are directly proportional to the dose.<sup>4,6,11</sup> Zoledronic acid is rapidly and completely cleared from the plasma. The plasma concentration at 24 hours is less than 1% of peak levels. Following intravenous infusion, zoledronic acid concentrations decline in a triphasic fashion. The early distribution and elimination half-lives are 0.23 hours and 1.75 hours, respectively. The terminal elimination half-life is 167 hours. In contrast, the terminal half-life of pamidronate is 28 hours. Approximately 44% of an administered dose of zoledronic acid is recovered unchanged in the urine within 24 hours. The remainder is taken up into bone and slowly released back into the plasma over the terminal half-life. Zoledronic acid is eliminated unchanged in the urine. Renal clearance of zoledronic acid is 82% of creatinine clearance.

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## Clinical Trials

### *Hypercalcemia of Malignancy*

The efficacy of zoledronic acid in treating HCM was compared to pamidronate in two randomized, controlled, multicenter, double blind, international, clinical trials.<sup>12</sup> The data from these studies were pooled for analysis. Eligible patients were required to have a baseline corrected serum calcium (CSC) of at least 12 mg/dL (3 mm/dL). A total of 275 patients were randomized to treatment with zoledronic acid 4 mg (n=86), zoledronic acid 8 mg (n=90), and pamidronate 90 mg (n=99). Patients were followed for 56 days or until relapse, defined as a CSC of at least 11.6 mg/dL. Patients were considered to have refractory disease if the CSC was not lower than baseline by 0.2 mg/dL on day 4 or 1.0 mg/dL on day 7, or day 10 CSC was > 11.2 mg/dL. Patients with refractory or relapsed disease were treated with zoledronic acid 8 mg. The primary endpoint was the day 10 response.

On day 10 a complete response (CSC < 10.8 mg/dL) was seen in 88.4% (76/86; p=0.002 vs pamidronate) of the patients in the zoledronic acid 4 mg arm, 86.7% (78/90; p=0.015) of those receiving zoledronic acid 8 mg, and 69.7% (69/99) in the pamidronate 90 mg group. On day 4, a complete response was seen in 45.6% (p=NS), 55.6% (p=0.021), and 33.3% of the zoledronic acid 4 mg, zoledronic acid 8 mg, and pamidronate arms, respectively. On day 7, the complete response rates were zoledronic acid 4 mg 82.6% (p=0.005), zoledronic acid 8 mg 83.3% (p=0.01), and pamidronate 63.6%. In patients whose CSC normalized following treatment, the median durations of complete response were 32 days, 43 days, and 18 days for zoledronic acid 4 mg (p<0.05), zoledronic acid 8 mg patients, and pamidronate, respectively. In the 69 patients who received zoledronic acid 8 mg for relapsed or refractory HCM, the mean CSC dropped from 12.67 mg/dL to 10.84 mg/dL at day 10. A complete response was obtained in 36 of these patients (52%) at day 10. The median duration of response was 15 days and the median time to relapse was 8 days. The rates of adverse events including fever, anemia, nausea, constipation and dyspnea were similar amongst the three groups. Common Toxicity Criteria grade 3 or 4 serum creatinine values (increase in serum creatinine > 3 times the upper limit of normal) were reported in two (2.3%) zoledronic acid 4 mg recipients, five (5.2%) zoledronic acid 8 mg recipients, and four (4%) pamidronate patients.

### *Metastatic Bone Disease*

Zoledronic acid has been shown to be as effective as pamidronate in preventing skeletal-related events in patients with bone lesions due to metastatic breast carcinoma or multiple myeloma.<sup>13</sup> Eligible patients had to have Durie-Salmon stage III multiple myeloma and at least one osteolytic bone lesion or breast cancer with at least one osteolytic/mixed bone lesion. Patients with hypercalcemia (CSC >12 mg/dL) were excluded. Patients were randomized in a double-blind fashion

to treatment with zoledronic acid 4 mg (n=564), zoledronic acid 8 mg (n=526), or pamidronate 90 mg (n=558) every 3 to 4 weeks for 13 months. Following an interim analysis the dose for subsequent treatments in the 8-mg zoledronic acid group was reduced to 4 mg because of concerns over renal toxicity. This group is referred to as the zoledronic acid 8/4 mg arm. The primary endpoint was the proportion of patients experiencing at least one skeletal-related event during the study period. Skeletal-related events were defined as pathological fractures, spinal cord compression, radiation therapy or surgery to the bone. The proportions of patients experiencing at least one skeletal-related event were similar between treatment groups. The incidence of skeletal-related events were 47% (86/183), 49% (79/160), and 49% (82/167) in the zoledronic acid 4-mg, zoledronic acid 8/4-mg, and pamidronate arms, respectively. The annual rate of skeletal events was 1.23+3.98 for zoledronic acid 4-mg, 1.08+1.99 for zoledronic acid 8/4-mg, and 1.40+4.31 for pamidronate. The annual rates of skeletal events plus HCM were 1.13+3.98, 1.08+1.99, and 1.47+4.40 for zoledronic acid 4-mg, zoledronic acid 8/4mg, and pamidronate 90-mg, respectively. The incidences of the most common side effects (bone pain, nausea, fatigue, and fever) were similar in the three groups. Abnormal serum creatinine levels were more common in the zoledronic acid 8/4 mg group than the zoledronic 4 mg or pamidronate groups.

Zoledronic acid was also found to be as effective as pamidronate in reducing the need for radiotherapy. In a double blind, dose-response study of zoledronic acid vs pamidronate in the treatment of osteolytic lesions due to metastatic breast carcinoma or multiple myeloma.<sup>14</sup> A total of 280 patients with malignant osteolytic disease were randomized to treatment with zoledronic acid 0.4 mg (n=68), 2 mg (n=73), or 4 mg (n=66) or pamidronate 90 mg (n=73). The proportion of patients receiving radiation to the bone was 24% (n=16), 19%(n=14), 21% (n=14) and 18% (n=13) in the zoledronic acid 0.4-, 2-, and 4-mg and pamidronate 90 mg groups, respectively. The reductions in the need for radiation were statistically significant in the 2- and 4-mg doses of zoledronic acid and the 90-mg dose of pamidronate (p<0.05). The effect of zoledronic acid 0.4 mg on the need for radiation was not significant (p=0.104). The combined endpoint of skeletal-related events of any kind and hypercalcemia also occurred less frequently in patients treated with zoledronic acid 2 mg (25%, n=35) or 4 mg (22%, n=33) or pamidronate (22%, n=30) than with 0.4 mg zoledronic acid (46%, n=31). Increases in lumbar spine BMD (6.2-9.6%) and decreases in the bone resorption marker N-telopeptide (range, -37.1 to -60.8%) were observed for all treatment groups. The most common adverse effects were skeletal pain, fatigue nausea, vomiting, and headache all of which were similar in severity and frequency in all treatment groups.

### Osteoporosis

Oral bisphosphonates are routinely used for the prevention and treatment of osteoporosis. Intermittent administration of pamidronate has also been tried as an alternative agent in patients who are unable to tolerate or unable to comply with oral regimens. A typical maintenance dose is 30 mg infused over one hour every 3 months. Zoledronic acid has been investigated as a single annual treatment for postmenopausal osteoporosis. A total of 351 women with T-scores of less than -2 were randomized in a double-blind fashion to one of six treatment arms: zoledronic acid 0.25, 0.5, or 1 mg every 3 months; zoledronic acid 2 mg at months 0 and 6; zoledronic acid 4 mg at month 0; or a normal saline placebo control. At the completion of the year-long trial the patients treated with zoledronic acid had significantly greater increases in bone mineral density in both the lumbar spine and femoral neck than those treated with placebo. The increases in bone mineral density values for the spine were 4.3 to 5.1% higher for zoledronic acid than placebo ( $p < 0.001$ ). Increases in bone mineral density for the femoral neck were 3.1 to 3.5% higher among the zoledronic acid groups than placebo ( $p < 0.01$ ). Serum C-telopeptide levels decreased 49 to 52% and 8% in the zoledronic acid and placebo groups, respectively ( $p < 0.01$ ). The ratio of urinary N-telopeptide to creatinine decreased 54 to 65% with zoledronic acid compared to a 3% increase with placebo ( $p < 0.01$ ).

### Adverse Effects

The adverse reactions associated with zoledronic acid in clinical trials were typically mild and transient.<sup>11</sup> The most commonly reported side effects included fever, nausea, constipation, anemia, and dyspnea (see Table 1). The incidence and severity of these reactions were generally similar for zoledronic acid and pamidronate.<sup>12,13</sup> Grade 3-4 serum creatinine abnormalities occurred in 3.5% of patients treated with zoledronic acid and 6% of patients receiving pamidronate.<sup>11</sup> Renal toxicity can be minimized by adequately hydrating the patient prior to and during zoledronic acid therapy, not exceeding a maximum dose of 4 mg and infusing each dose over a minimum of 15 minutes.

### Cost, Dose, How Supplied

The recommended dose of zoledronic acid is 4 mg intravenously over 15 minutes. Patients should be adequately hydrated while receiving zoledronic acid. In patients whose serum calcium fails to normalize or who experience recurrence of HCM, the dose may be repeated as needed at intervals of no less than 7 days. The optimal frequency for redosing has not been established, but in clinical trials of HCM the duration of action of zoledronic acid was approximately twice that of pamidronate.

**Table 1.**  
*Adverse Events Reported in Clinical Trials of Zoledronic Acid*<sup>11</sup>

Adverse Event	Zoledronic acid 4 mg (%)	Pamidronate 90 mg (%)
Fever	44.2	33.0
Nausea	29.1	27.2
Constipation	26.7	12.6
Diarrhea	17.4	16.5
Abdominal Pain	16.3	12.6
Vomiting	14.0	16.5
Anorexia	9.3	13.6
Hypotension	10.5	1.9
Anemia	22.1	17.5
Hypophosphatemia	12.8	1.9
Hypokalemia	11.6	15.5
Hypomagnesemia	10.5	4.9
Skeletal pain	11.6	9.7
Insomnia	15.1	9.7
Anxiety	14.0	7.8
Confusion	12.8	12.6
Agitation	12.8	7.8
Dyspnea	22.1	19.4
Coughing	11.6	11.7

Zoledronic acid is supplied in 4-mg, single-dose vials. Following reconstitution with sterile water for injection the dose should be further diluted with 100 mL of normal saline or 5% dextrose injection. Zoledronic acid should not be mixed with solutions containing calcium, including products such as Lactated Ringer's.

The average acquisition price for zoledronic acid 4-mg is \$744.81 (AWP of \$953.61). In contrast, the average acquisition price for the now generically available pamidronate 90-mg is approximately \$300. Converting patients to zoledronic acid would result in an extra expense of over \$400 per treatment in drug costs. Some of the increased expense is offset by a decrease in nursing time and the potential for more efficient through-put of patients. Evidence from the clinical trials suggests that zoledronic acid may have a longer duration of action than pamidronate. If this were supported in clinical practice, the need for fewer doses would further reduce the net impact of zoledronic acid.

### Conclusion

Zoledronic acid is a new intravenous bisphosphonate that offers some advantage over pamidronate insofar as it requires less administration time and may increase patient convenience and reduce nursing time. If the longer duration of action and

increased response rate seen in clinical trials are also seen in general practice, zoledronic acid may also have some clinical advantages over pamidronate. Economic analyses of zoledronic acid must balance the increased drug costs against the potential for increased efficiencies that may be achieved by reducing administration times.

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