Zometa®

(zoledronic acid for injection)

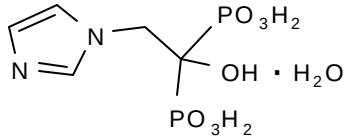
For Intravenous Infusion

Rx only

Prescribing Information

DESCRIPTION

Zometa®, contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1g/Mol. Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Zometa® (zoledronic acid for injection) is available in vials as a sterile powder for reconstitution for intravenous infusion. Each vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis .

Inactive Ingredients: mannitol, USP, as bulking agent, and sodium citrate, USP, as buffering agent.

CLINICAL PHARMACOLOGY

General

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Preclinical data indicate that low micromolar concentratio ns of zoledronic acid are cytostatic and pro-apoptotic *in vitro* to a range of human cancer cell lines (breast, prostate, lung, bladder, myeloma), and that this anti-tumor efficacy can be synergistically enhanced by combination with other anti-cancer drugs . Zoledronic acid is also anti-proliferative for human fetal osteoblasts and promotes their differentiation, a property potentially relevant for the treatment of bone metastases in prostate cancer. Zoledronic acid inhibits the proliferation of human endothelial cells *in vitro* and is anti-angiogenic *in vivo*. Zoledronic acid at picomolar concentrations inhibits tumor cell invasion through extracellular matrix.

Pharmacokinetics

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa® (zoledronic acid for injection) were given to 3264 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of Cmax after 24 hours post infusion with, showing population half-lives of $t_{½\alpha}$ 0.230.24 hours and $t_{½\beta}$ 1.751.87 hours for the early disposition phases of the drug, and followed by a prolonged period of very low concentrations in plasma between days 2 and 28 post infusion, distribution and elimination of the drug, andwith a terminal elimination half-life $t_{½\gamma}$ of 167146 hours. describing the low concentrations in plasma observed up to 28 days post dose. The area under the plasma concentration versus time curve ($AUC_{0\text{-}24h}$) of zoledronic acid was linearly related to dose. The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0\text{-}24h}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and ex vivo studies of zoledronic acid showed no low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was low (approximately 56%22 %) and independent of the concentration of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is primarily eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, the radioactivity excreted in the urine consisted solely of intact drug.

Excretion

In 64a study in patients with cancer and bone metastases (n=32), 44 ± 18% on average (± s.d.) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations days 2 to 28 post dose. 167-hour terminal half-life in plasma. The area under the plasma concentration versus time curve of zoledronic acid was linearly related to dose, and the cumulative percent of drug excreted in the urine 0-24 hours was independent of dose. The 0 – 24 hour renal clearance of zoledronic acid in these patients was on average (± s.d.) 3.7 ± 2.0 L/h. 4.0 ± 2.3 L/h, and the plasma clearance, representing renal elimination plus uptake by bone, was 5.6 ± 2.5 L/h.

Zoledronic acid clearance was independent of dose, and demographic variables. Effects of body weight, gender, and race on clearance were within the bounds of the inter-patient variability of clearance, which was 36%. not affected by body weight, body mass index, or gender. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=35) to 15 minutes (n=47) resulted in a 30%34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 393 403 ± 100118 ng/mL vs 267264 ± 4186 ng/mL) and a 21%10% increase in the total AUC (412378 ± 107116 ng x h/mL vs 496420 ± 212218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pharmacokinetic data in patients with hypercalcemia are not available.

Pediatrics: Pharmacokinetic data in pediatric patients are not available.

Geriatrics: The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases who ranged in age from 40 38 years to 85 84 years.

Race: The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases.

Hepatic Insufficiency: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Insufficiency: Limited pharmacokinetic data are available for ZOMETA® in patients with severe renal impairment (creatinine clearance <30 mL/min). The pharmacokinetic studies were conducted in cancer patients (n=64) typical of the target clinical population, showing renal function mainly in the range of normal to moderately impaired [mean (± s.d.) creatinine clearance 84 ± 29 mL/min, range 22–143 mL/min]. In these 64 patients the renal clearance of zoledronic acid was found to closely correlate with creatinine clearance, representing in the mean (± s.d.) 75 ± 33% of the creatinine clearance. Patients with mild to moderate renal impairment (creatinine clearance 50–80 mL/min) showed increases in plasma AUC of 26% to 36%, whereas patients with moderate to severe renal impairment (creatinine clearance 30–50 mL/min) showed increases in plasma AUC of 27% to 41%, compared to patients with normal renal function (creatinine clearance > 80 mL/min). However, there were no further increases in the systemic exposure after multiple Zometa doses in patients with impaired renal function. *See Precautions.*

~~*Renal Insufficiency:* Pharmacokinetic data are not available for zoledronic acid in patients with severe renal impairment. In a pharmacokinetic study in patients with cancer and bone metastases (n=32) who had normal to moderately impaired renal function [mean baseline creatinine clearance of 81 ± 30 mL/min (4.9 ± 1.8 L/h)], the renal clearance of zoledronic acid was found to closely correlate with creatinine clearance. On average, zoledronic acid clearance in these patients was 82 ± 35% of the creatinine clearance. (See PRECAUTIONS, Renal Insufficiency.)~~

Pharmacodynamics

Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Reducing excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

Patients who have hypercalcemia of malignancy can generally be divided into two groups according to the pathophysiologic mechanism involved: humoral hypercalcemia and hypercalcemia due to tumor invasion of bone. In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE AND ADMINISTRATION).

Clinical Trials

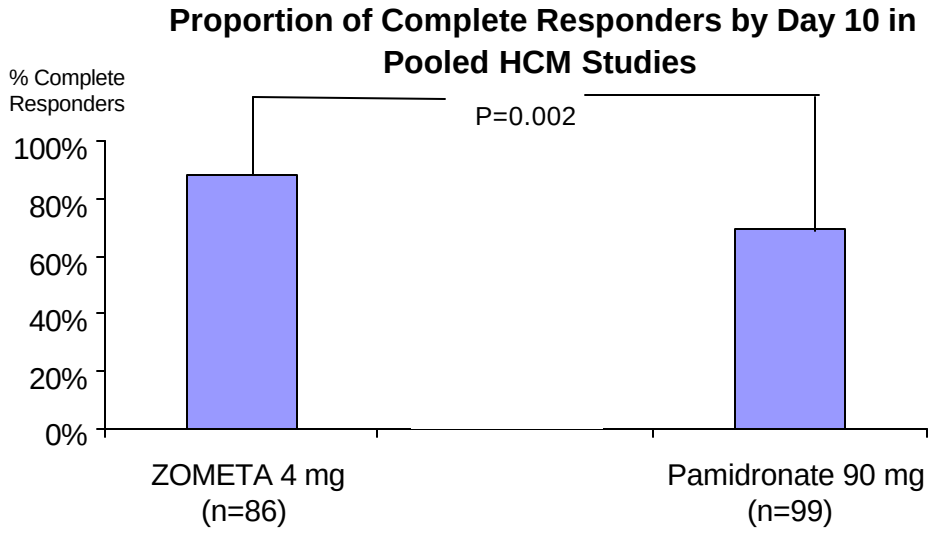
Hypercalcemia of Malignancy

Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). **NOTE: Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes. (See WARNINGS and DOSAGE AND ADMINISTRATION.**) The treatment groups in the clinical studies were generally well balanced with regards to age, sex, race, and tumor types. The mean age of the study population was 59 years; 81% were Caucasian, 15% were Black, and 4% were of other races. Sixty percent of the patients were male. The most common tumor types were lung, breast, head and neck, and renal.

In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of ≥12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to ≤ 10.8 mg/dL (2.70 mmol/L) within 10 days after drug infusion.

To assess the effects of Zometa versus those of pamidronate, the two multicenter HCM studies were combined in a pre-planned analysis. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for Zometa 4 mg and pamidronate 90 mg, respectively (p=0.002). (see Figure 1) **In these studies, no additional benefit was seen for Zometa 8 mg over Zometa 4 mg; however, the risk of renal toxicity of Zometa 8 mg was significantly greater than that seen with Zometa 4 mg.**

Figure 1



Secondary efficacy variables from the pooled HCM studies included the proportion of patients who had normalization of corrected serum calcium (CSC) by Day 4; the proportion of patients who had normalization of CSC by Day 7; time to relapse of HCM; and duration of complete response. Time to relapse of HCM was defined as the duration (in days) of normalization of serum calcium from study drug infusion until the last CSC value <11.6 mg/dL (<2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC ≤ 10.8 mg/dL (2.70 mmol/L). The results of these secondary analyses for Zometa 4 mg and pamidronate 90 mg are shown in Table 1.

Table 1. Secondary Efficacy Variables in Pooled HCM Studies

	Zometa® 4mg		**Pamidronate 90mg**	
Complete response	N	Response rate	N	Response rate
By Day 4	86	45.3%	99	33.3%
By Day 7	86	82.6%*	99	63.6%
Duration of response	N	Median duration (days)	N	Median duration (days)
Time to relapse	86	30*	99	17
Duration of complete response	76	32	69	18

*P less than 0.05 vs. pamidronate 90 mg

Osteolytic, Osteoblastic and Mixed Bone Metastases of Solid Tumor and Osteolytic Lesions of Multiple Myeloma

Osteolytic bone lesions and metastases commonly occur in patients with multiple myeloma, breast cancer, non-small cell lung cancer, renal cell carcinoma and a variety of other solid tumors. Bone metastases from prostate carcinoma classically are osteoblastic in contrast to those from other carcinomas, which are usually osteolytic

or mixed osteolytic/osteoblastic. These cancers demonstrate a phenomenon known as osteotropism, meaning they possess an extraordinary affinity for bone. The distribution of osteolytic bone metastases in these cancers is predominantly in the axial skeleton, particularly the spine, pelvis, and ribs, rather than the appendicular skeleton, although lesions in the proximal femur and humerus are not uncommon. This distribution is similar to the red bone marrow in which slow blood flow possibly assists attachment of metastatic cells. The surface-to-volume ratio of trabecular bone is much higher than cortical bone, and therefore disease processes tend to occur more floridly in trabecular bone than at sites of cortical tissue. Adenocarcinoma of the prostate spreads most commonly to the well vascularized areas of the skeleton such as the vertebral column, ribs, skull, and the proximal ends of the long bones. Prostate carcinoma cells have long been believed to gain access to the vertebral column and ribs via the Batson venous plexus, which is a low pressure, high volume plexus of vertebral veins that join the intercostal veins.

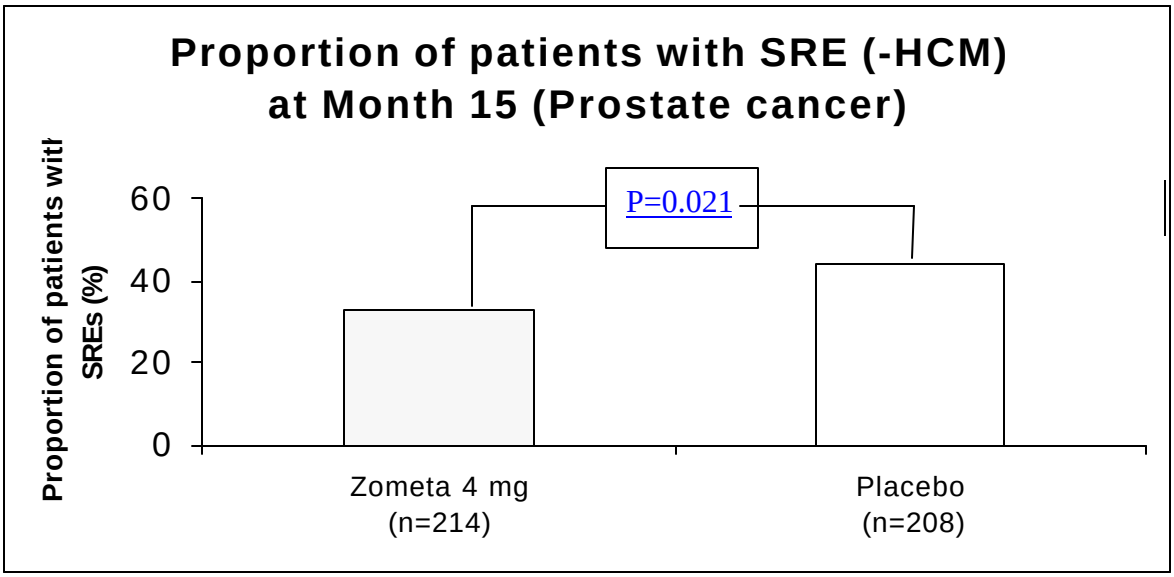
These bone changes in patients with evidence of osteolytic and osteoblastic skeletal destruction may cause severe bone pain that requires either radiation therapy or narcotic analgesics (or both) for symptomatic relief. These changes also cause pathologic fractures of bone in both the axial and appendicular skeleton. Axial skeletal fractures of the vertebral bodies may lead to spinal cord compression or vertebral body collapse with significant neurologic complications. Patients may also experience episode(s) of hypercalcemia.

Clinical Trials

Prostate Cancer Bone Metastases:

In a phase III randomized, double-blind trial, ZOMETA was compared to placebo for the prevention of Skeletal Related Events (SREs) in prostate cancer patients with bone metastases. SREs were defined as pathological fractures, spinal cord compression, radiation therapy to bone, surgery to bone, or need to change chemotherapy. A total of 422 men (214 ZOMETA 4 mg, 208 placebo) with metastatic bone disease from prostate cancer with a rising serum PSA despite hormonal treatment were randomized to receive either ZOMETA 4 mg administered over 15 minutes or placebo every 3 weeks for 15 months. The primary efficacy variable was the proportion of patients having a SRE during 15 months of treatment. The proportion of patients experiencing at least one SRE (33% for ZOMETA 4 mg vs. 44% for placebo, p = 0.021) demonstrated statistically significant superiority for Zometa vs. placebo. See Figure 2.

Figure 2



ZOMETA was statistically significantly superior to placebo for time to first SRE (median of 321 days for placebo vs. median not reached for ZOMETA 4 mg, p = 0.011) , and Skeletal Morbidity Rate (Number of SREs/time, mean of 0.80 for ZOMETA 4 mg vs. 1.5 for placebo, p = 0.006) . Zometa demonstrated a statistically significant superiority over placebo for time to fracture (p=0.011) and skeletal morbidity rate for fractures (number of SREs/time, 0.22 for Zometa 4 mg and 0.45 for placebo (p=0.009). See Table 2.

Table 2: Results of the secondary efficacy variables

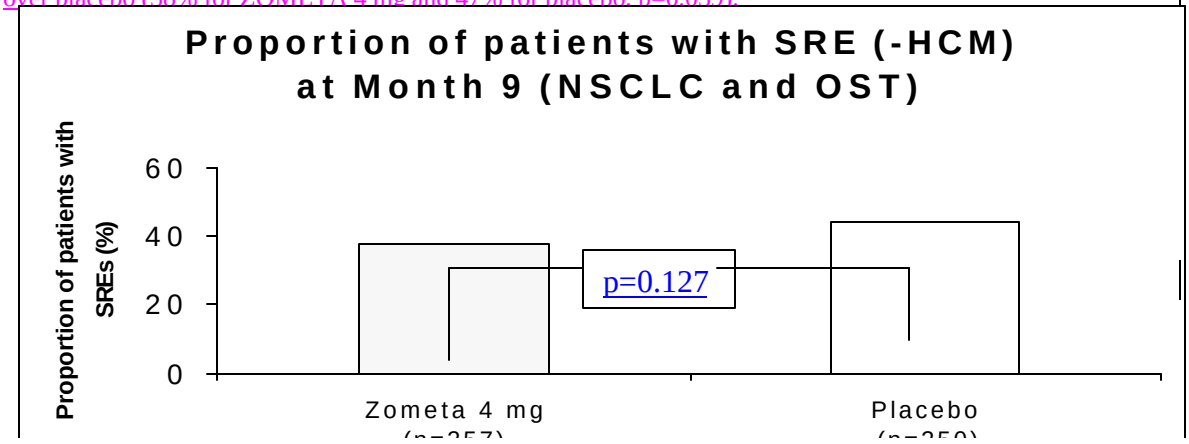
Prostate Cancer Patients Receiving Hormonal Therapy

	All SRE (-HCM)		Fractures*		Radiation Therapy to Bone	
	ZOMETA 4 mg	Placebo	ZOMETA 4 mg	Placebo	ZOMETA 4 mg	Placebo
N	214	208	214	208	214	208
Median Time to SRE (days)	NR**	321	NR**	NR**	NR**	NR**
P-Value	0.011		0.011		0.081	
Skeletal Morbidity Rate (#SRE/year) Mean	0.8	1.5	0.21	0.45	0.44	0.88
P-Value	0.006		0.009		0.084	

*Includes vertebral and non-vertebral fractures
**NR=Not Reached

Lytic metastases from solid tumors other than breast cancer or prostate cancer

A second phase III randomized, double-blind, placebo-controlled trial compared Zometa to placebo for the prevention of SREs in patients who had solid tumors other than breast cancer or prostate cancer with osteolytic or mixed bone metastases. SREs were defined as pathological fractures, spinal cord compression, radiation therapy to bone, and surgery to bone. Patients had to have ≥ 1 lytic metastasis for study entry. A total of 257 patients were randomized to ZOMETA; 134 patients with non-small cell lung cancer (NSCLC) and 123 with other solid tumors (OST). A total of 250 patients were randomized to placebo (130 patients with NSCLC, 120 with OST). Patients received either a 15-minute intravenous infusions of ZOMETA 4 mg or placebo every 3 weeks for nine months. The primary efficacy variable was the proportion of patients having a SRE during nine months of treatment. By 9 months the ZOMETA 4 mg group had a lower proportion of patients experiencing a SRE when compared to placebo (38% for ZOMETA 4 mg, 44% for placebo, p=0.127), see Figure 3. The difference was not statistically significant when patients with hypercalcemia are excluded from the analysis. When HCM is included, the proportion of patients having an SRE reached statistical significance favoring ZOMETA 4 mg over placebo (38% for ZOMETA 4 mg and 47% for placebo, p=0.039).



Proportion of patients with SRE (-HCM) at Month 9 (NSCLC and OST)

Study patients had a median overall survival of 6 months. ZOMETA extended the time to a SRE by over two months (median of 230 days vs. 163 days, p = 0.023). ZOMETA also extended the time to fracture (p=0.031) and time to radiation therapy to bone (p=0.051), see Table 3.

Table 3: Results of the secondary efficacy variables

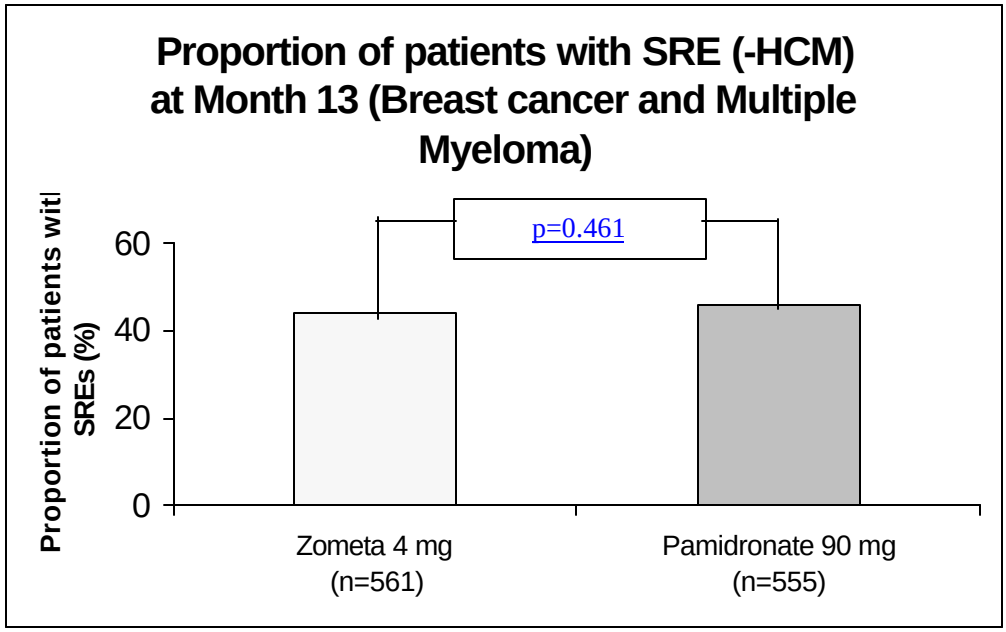
	NSCLC and OST Patients					
	All SRE (-HCM)		Fractures*		Radiation Therapy to Bone	
	ZOMETA 4 mg	Placebo	ZOMETA 4 mg	Placebo	ZOMETA 4 mg	Placebo
N	257	250	257	250	257	250
Median Time to SRE (days)	230	163	NR**	NR**	314	272
P-Value	0.023		0.031		0.051	
Skeletal Morbidity Rate (#SRE/year) Mean	2.24	2.52	0.43	0.66	1.70	1.89
P-Value	0.069		0.113		0.118	

*Includes vertebral and non-vertebral fractures
**NR=Not Reached

Breast Cancer Bone Metastases and Bone Lesions of Multiple Myeloma

The third phase III randomized, double-blind trial was designed to demonstrate comparable efficacy of ZOMETA 4 mg to pamidronate 90 mg. A total of 1,122 patients (564 ZOMETA 4 mg, 558 pamidronate 90 mg) with either Durie-Salmon Stage III multiple myeloma or Stage IV breast cancer with at least one bone lesion were treated with ZOMETA 4 mg via 15-minute intravenous (IV) infusion or pamidronate 90 mg via 2-hour IV infusion every 3 to 4 weeks for 12 months. The primary efficacy endpoint was the proportion of patients experiencing at least one skeletal-related event (SRE) by 13 months. The proportion of patients were 44% and 46% for ZOMETA 4 mg and pamidronate 90 mg, respectively (p=0.461). See Figure 4.

Figure 4



There were no significant differences between ZOMETA and pamidronate in the skeletal morbidity rate for all SREs excluding hypercalcemia or skeletal morbidity rate for fractures. There were no significant differences between ZOMETA and pamidronate in time to first SRE excluding hypercalcemia or time to first fracture. There was a significant difference favoring ZOMETA 4 mg over pamidronate 90 mg for the time to first radiation to bone and this was also true for the skeletal morbidity rate for radiation to bone. See Table 4.

Table 4: Results of the secondary efficacy variables

Breast Cancer and Multiple Myeloma Patients

	All SRE (-HCM)		Fractures*		Radiation Therapy to Bone	
	ZOMETA 4 mg	Pamidronate 90 mg	ZOMETA 4 mg	Pamidronate 90 mg	ZOMETA 4 mg	Pamidronate 90 mg
N	561	555	561	555	561	555
Median Time to SRE (days)	373	363	448	399	504	NR**
P-Value	0.322		0.658		0.019	
Skeletal Morbidity Rate (#SRE/year) Mean	1.13	1.40	0.62	0.66	0.47	0.71
P-Value	0.197		0.712		0.018	

* Includes vertebral and non-vertebral
**NR=Not Reached

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Zometa® (zoledronic acid for injection) is indicated for the treatment of hypercalcemia of malignancy.

Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia. The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

Osteolytic, Osteoblastic, and Mixed Bone Metastases of Solid Tumors and Osteolytic Lesions of Multiple Myeloma

ZOMETA is indicated for the treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.

CONTRAINDICATIONS

Zometa® (zoledronic acid for injection) is contraindicated in patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of Zometa.

WARNINGS

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA SHOULD NOT EXCEED 4 MG AND THE DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES.

Bisphosphonates, including Zometa® (zoledronic acid for injection), have been associated with renal toxicity manifest as deterioration of renal function and potential renal failure. In clinical trials, the risk for renal function deterioration (defined as an increase in serum creatinine) was significantly increased in patients who received Zometa over 5 minutes compared to patients who received the same dose over 15 minutes. In addition, the risk for renal function deterioration and renal failure was significantly increased in patients who received Zometa 8 mg, even when given over 15 minutes. While this risk is reduced with the 4 mg ZOMETA dose administered over 15 minutes, deterioration in renal function can still occur. Risk factors for this deterioration include elevated baseline creatinine, age >60, and multiple cycles of treatment with the bisphosphonate. Patients who receive Zometa should have standard laboratory and clinical parameters of renal function assessed prior to treatment and periodically after treatment to monitor for deterioration in renal function. (See PRECAUTIONS)

During the bone metastases trials, an amendment was introduced that required monitoring of serum creatinine prior to each dose of study drug. The following criteria were used in patients who needed to be retreated with ZOMETA:

~~The following criteria should be applied in patients who require retreatment with Zometa for HCM and who experience a decrease in renal function after receiving Zometa:~~

- If patients have a normal serum creatinine prior to treatment with Zometa® but have an increase of 0.5 mg/dL within two weeks of their next dose, Zometa should be withheld until the serum creatinine is at least within 10% of their baseline value.
- If patients have an abnormal serum creatinine prior to treatment with Zometa® but have an increase of 1.0 mg/dL within two weeks of their next dose, Zometa should be withheld until the serum creatinine is at least within 10% of their baseline value.

In the prostate cancer trial (scheduled study treatment duration, 15 months), the proportion of patients receiving ZOMETA 4 mg over 15 minutes who had a predefined increase in serum creatinine was 15.2% in the ZOMETA 4 mg group and 11.5% in the placebo group (risk ratio for ZOMETA 4 mg: 1.066). In the trial conducted in patients with solid tumors other than breast cancer or prostate cancer (scheduled study treatment duration, 9 months), the proportion with a predefined serum creatinine increase for ZOMETA 4 mg over 15 minutes was 10.9% compared to 6.7% in the placebo group (risk ratio for ZOMETA 4 mg: 1.571). Finally, in the trial conducted in patients with breast cancer or multiple myeloma (scheduled study treatment duration, 12 months), the proportion of patients receiving ZOMETA 4 mg over 15 minutes who had a pre-defined increase in serum creatinine was 8.8% compared to 8.2% of the patients receiving pamidronate 90 mg (risk ratio for ZOMETA 4 mg: 0.984). There were no statistically significant differences in the comparisons of Kaplan-Meier estimates of time to first renal function deterioration, between the ZOMETA patient groups receiving 4 mg over 15 minutes and their controls, in any of the three trials. Also, in these trials, the risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving ZOMETA (4 mg over 15 minutes), placebo, or pamidronate, an overall pattern consistent with this risk representing a time-dependent (but not strongly treatment-related) event in these patient populations.

Renal function should be monitored appropriately, considering individual risk factors, and patients with evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of continued treatment with ZOMETA outweighs the possible risk.

~~The potential risk for renal failure with subsequent dosing with Zometa must be very carefully weighed against the potential benefits of treatment and other available treatment options and consideration should be given to whether potential benefit with Zometa outweighs possible risk.~~

PRECAUTIONS

General

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zometa® (zoledronic acid for injection). If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Patients must be adequately rehydrated prior to administration of Zometa. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zometa in order to avoid hypocalcemia.

Renal Insufficiency:

Limited clinical data are available regarding use of Zometa in patients with renal impairment. Zometa is excreted primarily via the intact kidney and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Renal function should be closely monitored in all patients treated with Zometa.

Studies of Zometa in the treatment of hypercalcemia of malignancy excluded patients with serum creatinine ≥ 400 µmol/L or ≥ 4.5 mg/dL. No clinical or pharmacokinetics data are available to guide dose selection or to provide guidance on how to safely use Zometa in patients with severe renal impairment. Zometa should be

used in patients with severe renal impairment only if the expected clinical benefits outweigh the risk of renal failure and after considering other available treatment options. (See WARNINGS.) Dose adjustments of ZOMETA® are not necessary in patients presenting with mild to moderate renal impairment prior to initiation of therapy (serum creatinine < 400 µmol/L or < 4.5 mg/dL, or calculated creatinine clearance by Cockcroft-Gault formula of <30 mL/min). In view of the potential impact of bisphosphonates, including Zometa, on renal function, the lack of extensive clinical safety data in patients with severe renal impairment at baseline (serum creatinine > 400 µmol/L or >4.5 mg/dL) and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance <30 mL/min), the use of Zometa is not recommended in this population.

In any patient requiring repeated administration of Zometa for hypercalcemia of malignancy, serum creatinine must be evaluated prior to each dose. Patients with evidence of deterioration in renal function should be appropriately evaluated and consideration should be given as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk. (See WARNINGS.)

Hepatic Insufficiency:

Only limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use Zometa in these patients.

Patients with Asthma:

While not observed in clinical trials with Zometa, administration of other bisphosphonates has been associated with bronchoconstriction in aspirin-sensitive asthmatic patients. Zometa should be used with caution in patients with aspirin-sensitive asthma.

Laboratory Tests

Serum calcium, electrolytes, phosphate, magnesium and creatinine, and CBC, differential, and hematocrit/hemoglobin must be closely monitored in patients treated with Zometa . (See WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.)

Drug Interactions

In vitro studies indicate that zoledronic acid is approximately 22 ± 11% 56% bound to plasma proteins. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug. However, no *in vivo* drug interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This has not been reported in Zometa clinical trials. Caution should also be exercised when Zometa is used in combination with loop diuretics due to an increased risk of hypocalcemia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥ 0.002 times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at

doses ≤ 0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

Mutagenesis: Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genototxic in the *in vivo* rat micronucleus assay.

Impairment of Fertility: Female rats were given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group (with systemic exposure of 0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and high–dose group included an increase in preimplantation losses and a decrease in the number of implantations and live fetuses.

Pregnancy Category C

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥ 0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (with a systemic exposure of ≥ 0.07 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given a subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid- and high-dose groups (with systemic exposures of 2.4 and 4.8 times, respectively, the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (≤ 0.5 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas), no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥ 0.05 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Adverse maternal effects were associated with, and may have been caused by, drug–induced hypocalcemia.

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

Nursing Mothers

It is not known whether Zometa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zometa is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Zometa in pediatric patients have not been established.

Geriatric Use

Clinical studies of Zometa in hypercalcemia of malignancy included 34 patients who were 65 years of age or older No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zometa as compared to younger patients. However, because of the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients, Zometa should be administered with caution in this patient population.

Controlled clinical studies of ZOMETA in the treatment of osteolytic, osteoblastic and mixed bone metastases of solid tumor and osteolytic lesions of multiple myeloma in patients over age 65 revealed equal efficacy and safety. The proportion of patients experiencing SREs is lower in the ZOMETA treatment group when compared to placebo and similar to pamidronate 90 mg. Older patients generally had adverse events similar to those of the overall population. Renal adverse events occurred in similar proportions of patients with ZOMETA® or placebo.

However, because of the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients, Zometa® should be administered with caution in this patient population.

ADVERSE REACTIONS

Hypercalcemia of malignancy

Adverse reactions to Zometa® (zoledronic acid for injection) are usually mild and transient and similar to those reported for other bisphosphonates. Intravenous administration has been most commonly associated with fever. Occasionally, patients experience a flu-like syndrome consisting of fever, chills, bone pain and/or arthralgias, and myalgias. Gastrointestinal reactions such as nausea and vomiting have been reported following intravenous infusion of Zometa. Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Rare cases of rash, pruritis, and chest pain have been reported following treatment with Zometa.

As with other bisphosphonates, cases of conjunctivitis and hypomagnesemia have been reported following treatment with Zometa.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorous, and serum magnesium observed in two clinical trials of Zometa in patients with HCM are shown in Table 25.

Table 25: Grade 3-4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium Serum Phosphorous, and Serum Magnesium in Two Clinical Trials In Patients with HCM.

	Grade 3				Grade 4			
Laboratory Parameter	**Zometa® 4 mg**		**Pamidronate 90 mg**		**Zometa® 4 mg**		**Pamidronate 90 mg**	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine[1]	2/86	(2.3%)	3/100	(3.0%)	0/86	--	1/100	(1.0%)
Hypocalcemia[2]	1/86	(1.2%)	2/100	(2.0%)	0/86	--	0/100	--
Hypophosphatemia[3]	36/70	(51.4%)	27/81	(33.3%)	1/70	(1.4%)	4/81	(4.9%)
Hypomagnesemia[4]	0/71	--	0/84	--	0/71	--	1/84	(1.2%)

[1] Grade 3 (>3xUpper limit of Normal); Grade 4 (>6xUpper limit of Normal)
[2] Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3] Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4] Grade 3 (<0.8 mEq/L); Grade 4 (<0.5 mEq/L)

Table 36 provides adverse events that were reported by 10% or more of the 189 patients treated with Zometa 4 mg or pamidronate 90 mg from the two controlled multi-center HCM trials. Adverse events are listed regardless of presumed causality to study drug

Table 36: Percentage of Patients with Adverse Events 10%
Reported in Hypercalcemia of Malignancy Clinical Trials By Body System

	Zometa® 4 mg n (%)	Pamidronate 90 mg n (%)
Patients Studied		
Total no. of patients studied	86 (100)	103 (100)
Total no. of patients with any AE	81 (94.2)	95 (92.2)
Body as a Whole		
Fever	38 (44.2)	34 (33.0)
Progression of Cancer	14 (16.3)	21 (20.4)
Digestive		
Nausea	25 (29.1)	28 (27.2)
Constipation	23 (26.7)	13 (12.6)
Diarrhea	15 (17.4)	17 (16.5)
Abdominal Pain	14 (16.3)	13 (12.6)
Vomiting	12 (14.0)	17 (16.5)
Anorexia	8 (9.3)	14 (13.6)
Cardiovascular		
Hypotension	9 (10.5)	2 (1.9)
Hemic and Lymphatic System		
Anemia	19 (22.1)	18 (17.5)
Infections		
Moniliasis	10 (11.6)	4 (3.9)
Laboratory Abnormalities		
Hypophosphatemia	11 (12.8)	2 (1.9)
Hypokalemia	10 (11.6)	16 (15.5)
Hypomagnesemia	9 (10.5)	5 (4.9)
Musculoskeletal		
Skeletal Pain	10 (11.6)	10 (9.7)
Nervous		
Insomnia	13 (15.1)	10 (9.7)
Anxiety	12 (14.0)	8 (7.8)
Confusion	11 (12.8)	13 (12.6)
Agitation	11 (12.8)	8 (7.8)
Respiratory		
Dyspnea	19 (22.1)	20 (19.4)
Coughing	10 (11.6)	12 (11.7)
Urogenital		
Urinary Tract Infection	12 (14.0)	15 (14.6)

The following adverse events from the two controlled multi-center HCM trials (n=189) were reported by a greater percentage of patients treated with Zometa 4 mg than with pamidronate 90 mg and occurred with a

frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug.

Body as a Whole: asthenia, chest pain, leg edema, mucositis, metastases

Digestive System: dysphagia

Hemic and Lymphatic System: granulocytopenia, thrombocytopenia, pancytopenia

Infection: non-specific infection

Laboratory Abnormalities: hypocalcemia

Metabolic and Nutritional: dehydration

Musculoskeletal: arthralgias

Nervous System: headache, somnolence

Respiratory System: pleural effusion

NOTE: In the HCM clinical trials, pamidronate 90 mg was given as a 2-hour intravenous infusion. The relative safety of pamidronate 90 mg given as a 2-hour intravenous infusion compared to the same dose given as a 24-hour intravenous infusion has not been adequately studied in controlled clinical trials.

Osteolytic, Osteoblastic and Mixed Bone Metastases of Solid Tumor and Osteolytic Lesions of Multiple Myeloma

In general, Zometa was well tolerated across all studies for various tumor types in patients with bone metastases. The proportion of patients experiencing Grade 3 and Grade 4 laboratory abnormalities and adverse events were similar in patients treated with Zometa and pamidronate

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorous, and serum magnesium observed in four clinical trials of Zometa in patients with Bone Metastases are shown in Tables 7 and 8.

Table 7: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium Serum Phosphorous, and Serum Magnesium in Four Clinical Trials In Patients with Bone Metastases.

	Grade 3		
Laboratory Parameter	**ZOMETA® 4 mg** n/N (%)	**Pamidronate 90 mg** n/N (%)	**Placebo** n/N (%)
Serum Creatinine[1*]	7/529 (1.3%)	4/268 (1.5%)	2/241 (0.8%)
Hypocalcemia[2]	7/1041 (0.7%)	4/610 (0.7%)	0/415 --
Hypophosphatemia[3]	96/1041 (9.2%)	40/611 (6.5%)	13/415 (3.1%)
Hypomagnesemia[4]	0/1039 --	0/609 --	1/415 (0.2%)

[1] Grade 3 (>3xUpper limit of Normal); Grade 4 (>6xUpper limit of Normal)
[*] Zometa 4 mg infused over 15 minutes
[2] Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)

[3] Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4] Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Table 8: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium Serum Phosphorous, and Serum Magnesium in Four Clinical Trials In Patients with Bone Metastases.

	Grade 4		
Laboratory Parameter	**ZOMETA® 4 mg** n/N (%)	**Pamidronate 90 mg** n/N (%)	**Placebo** n/N (%)
Serum Creatinine[1]*	2/529 (0.4%)	1/268 (0.4%)	0/241 --
Hypocalcemia[2]	6/1041 (0.6%)	2/610 (0.3%)	1/415 (0.2%)
Hypophosphatemia[3]	6/1041 (0.6%)	0/611 --	1/415 (0.2%)
Hypomagnesemia[4]	2/1039 (0.2%)	2/609 (0.3%)	0/415 --

[1] Grade 3 (>3xUpper limit of Normal); Grade 4 (>6xUpper limit of Normal)
[*] Zometa 4 mg infused over 15 minutes
[2] Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3] Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4] Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

The most commonly reported (>15%) adverse experiences occurred with similar frequencies in the Zometa, pamidronate and placebo treatment groups, and most of these adverse experiences may have been related to the underlying disease state or cancer therapy. Table 9 lists the adverse experiences considered to be treatment-related in the bone metastases trials and occurred in ≥ 15% of patients.

Table 9: Commonly Reported Adverse Experiences in Four Controlled Clinical Trials

	Zometa 4 mg n (%)	Pamidronate 90 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients studied	1099 (100)	631 (100)	455 (100)
Total no. of patients with an AE	1081 (98.4)	622 (98.6)	444 (97.6)
Adverse events (preferred term)			
Bone pain	52.7%	54.7%	59.8%
Nausea	42.8%	44.7%	35.2%
Fatigue	35.9%	37.2%	27.5%
Vomiting NOS	29.8%	30.0%	25.1%
Pyrexia	29.7%	27.7%	18.2%
Anemia NOS	29.1%	26.9%	26.2%
Constipation	27.9%	23.5%	35.4%
Dyspnea NOS	24.0%	23.3%	20.4%
Diarrhea NOS	21.7%	24.9%	16.7%
Myalgia	21.1%	23.5%	14.9%
Weakness	21.1%	16.3%	23.1%
Anorexia	20.0%	12.0%	21.5%
Cough	19.3%	20.9%	12.5%
Edema lower limb	18.5%	18.2%	16.7%
Arthralgia	17.7%	17.3%	13.2%
Headache	17.6%	24.1%	10.3%
Malignant neoplasm aggravated	15.1%	11.3%	15.8%
Insomnia NEC	14.0%	16.8%	14.7%

NOS: Not otherwise specified NEC: Not elsewhere classified

Among the less frequently occurring adverse events (< 15% of patients), only rigors, hypokalemia, influenza-like illness, and hypocalcemia showed a trend for more events with bisphosphonate administration (Zometa 4 mg and pamidronate groups) compared to the placebo group. When interpreting these data, it should be kept in mind that the placebo group had the shortest overall exposure. However, all of these types of AEs have been previously reported with bisphosphonate treatment.

Less common adverse events reported more often with Zometa 4 mg than pamidronate included decreased weight, which was reported in 13.0% of patients in the Zometa 4 mg compared with 7.1% in the pamidronate group. The incidence of decreased weight, however, was similar for the placebo group (12.5%) and Zometa. Decreased appetite was reported in slightly more patients in the Zometa 4 mg (10.8%) compared with the pamidronate (7.3%) and placebo (8.6%) groups, but the clinical significance of these small differences is not clear.

Summary of chemotherapy toxicities

Table 10 is a summary of AEs commonly associated with chemotherapy toxicity that were reported in at least 1% of patients in any treatment group. Chemotherapy-associated AEs overall were reported in similar proportions of patients in the zoledronic acid and pamidronate groups, and in a lower proportion of patients in

the placebo group. A lower proportion (42.6%) of patients in the placebo group received antineoplastic treatment than patients in the other treatment groups (69.7% - 94.8%).

The majority of these adverse events were due to advanced cancer with aggravating factors of bone metastases and/or anti-neoplastic therapy. Nausea, vomiting, and anorexia were the most common types of chemotherapy-associated AEs. Anorexia and decreased appetite occurred in a slightly greater proportion of patients in the zoledronic acid 4 mg group than in the pamidronate group, but anorexia was most common in the placebo group. These minor differences are therefore likely to be due to disease rather than treatment effects.

Table 10. Percentage (%) of patients with chemotoxicity-associated AEs (³ 1%) – primary safety population

	Zol 4 mg n (%)	Pamidronate 90 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients studied	1099 (100)	631 (100)	455 (100)
Total no. of patients with a chemotoxicity AE	682 (62.1)	402 (63.7)	249 (54.7)
Adverse events (preferred term)			
Nausea	42.8%	44.7%	35.2%
Cytopenias	39.9%	39.3%	32.5%
Vomiting NOS	29.8%	30.0%	25.1%
Anorexia	20.0%	12.0%	21.5%
Alopecia	10.8%	13.2%	6.6%
Appetite decreased NOS	10.8%	7.3%	8.6%
Stomatitis	7.4%	9.7%	2.6%
Malaise	2.9%	2.2%	4.0%
Mouth ulceration	1.4%	1.1%	0.9%
Cachexia	0.7%	0.2%	1.8%
Malnutrition NOS	0.5%	0.8%	0.2%

NOS: Not otherwise specified

OVERDOSAGE

There is no experience of acute overdose with Zometa® (zoledronic acid for injection). Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

In controlled clinical trials, administration of Zometa 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zometa 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zometa 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy. **Single doses of Zometa should not exceed 4 mg and the duration of the intravenous infusion should be no less than 15 minutes. (See WARNINGS.)**

DOSAGE AND ADMINISTRATION

Hypercalcemia of malignancy

Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zometa® (zoledronic acid for injection). Vigorous saline hydration alone may be sufficient to treat mild, asymptomatic hypercalcemia.

The maximum recommended dose of Zometa in hypercalcemia of malignancy (albumin-corrected serum calcium* ≥12 mg/dL (3.0 mmol/L)) is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over **no less than 15 minutes**.

Patients should be adequately rehydrated prior to administration of Zometa. (See WARNINGS and PRECAUTIONS.)

Retreatment with Zometa 4 mg, may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zometa and possible deterioration in renal function must be assessed prior to retreatment with Zometa (See WARNINGS and PRECAUTIONS.)

*Albumin-corrected serum calcium (Cca, mg/dL) = Ca + 0.8 (mid-range albumin-measured albumin in mg/dL).

Osteolytic, Osteoblastic and Mixed Bone Metastases of Solid Tumor and Osteolytic Lesions of Multiple Myeloma

The recommended dose of ZOMETA in patients with solid tumors and osteolytic, mixed or osteoblastic bone metastases is 4 mg infused over 15 minutes.

The recommended dose of ZOMETA in patients with osteolytic, lesions of multiple myeloma is 4 mg infused over 15 minutes. ZOMETA has been frequently used with cyclophosphamide, doxorubicin, paclitaxel, anastrozole, melphalan and tamoxifen. It has been given less frequently with docetaxel, dexamethasone, prednisone, carboplatin, letrozole, vinorelbine, cisplatin and gemcitabine.

Preparation of Solution

Zometa is reconstituted by adding 5 mL of Sterile Water for Injection, USP, to each vial. The resulting solution allows for withdrawal of 4 mg of zoledronic acid. The drug must be completely dissolved before the solution is withdrawn.

The maximum recommended 4 mg-dose must be further diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. 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 should be refrigerated at 36°- 46°F (2-8°C). The total time between reconstitution, dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

Zometa must not be mixed with calcium-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.

Method of Administration **DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA SHOULD NOT EXCEED 4 MG AND THE DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES. (SEE WARNINGS)**

There must be strict adherence to the intravenous administration recommendations for Zometa in order to decrease the risk of deterioration in renal function.

***Note*: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

HOW SUPPLIED

Each vial contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP and 24 mg of sodium citrate, USP.

Carton of 1 vial NDC 0078-0350-84

Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F)

Manufactured by Novartis Pharma AG Basle, Switzerland

For Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936