NOVARTIS

T2005-72

Zometa®

(zoledronic acid) Injection

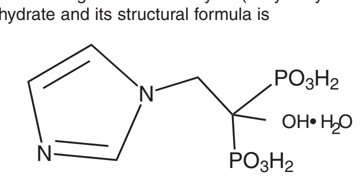
Concentrate for Intravenous Infusion

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) Injection is available in vials as a sterile liquid concentrate solution for intravenous infusion. Each 5-mL 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, water for injection 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.

Pharmacokinetics

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa® were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve ($AUC_{0\text{-}24h}$) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0\text{-}24h}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was 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 eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases on average (± 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. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL vs 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

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 38 years to 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: The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately-impaired renal function. Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for Zometa in patients with severe renal impairment (creatinine clearance <30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 mL/min. Creatinine clearance is calculated by the Cockcroft-Gault formula:

$$CrCl = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \quad \{x\ 0.85 \text{ for female patients}\}$$

Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, CL (L/h)=$6.5(CL_{cr}/90)^{0.4}$. These formulae can be used to predict the Zometa AUC in patients, where CL = Dose/$AUC_{0\text{-}\infty}$. The average $AUC_{0\text{-}24}$ in patients with normal renal function was 0.42 mg•h/L and the calculated $AUC_{0\text{-}\infty}$ for a patient with creatinine clearance of 75 mL/min was 0.66 mg•h/L following a 4-mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed. (See WARNINGS.)

Pharmacodynamics

Hypercalcemia of Malignancy

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.

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 STUDIES

Clinical Trials in Hypercalcemia of Malignancy

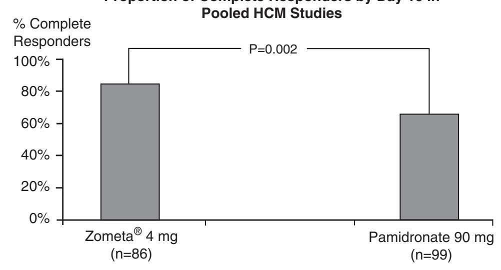
Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). **NOTE: Administration of Zometa 4 mg given 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

Proportion of Complete Responders by Day 10 in Pooled HCM Studies



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® 4 mg		Pamidronate 90 mg	
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.

Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors

Table 2 describes an overview of the efficacy population in three randomized Zometa trials in patients with multiple myeloma and bone metastases of solid tumors. These trials included a pamidronate-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in prostate cancer and a placebo-controlled study in other solid tumors. The prostate cancer study required documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy. The other placebo-controlled solid tumor study included patients with bone metastases from malignancies other than breast cancer and prostate cancer, listed in Table 3. These trials were comprised of a core phase and an extension phase. In trials 010 and 011, only the core phase was evaluated for efficacy as a high percentage of patients did not choose to participate in the extension phase. In study 039, both the core and extension phases were evaluated for efficacy showing the Zometa advantage during the first 15 months was maintained without decrement or improvement for 24 months. The design of the clinical trials 010, 011, and 039 does not permit assessment of whether more than one year administration of Zometa is beneficial. The optimal duration of Zometa administration is not known.

Table 2: Overview of Efficacy Population for Phase III Studies (Core Phase)

Study No.	No. of Patients	Median Duration (Planned Duration) Zometa® 4 mg	Zometa® Dose	Control	Patient Population
010	1,648	12.0 months (13 months)	4 and 8* mg Q3-4 weeks	Pamidronate 90 mg Q3-4 weeks	Multiple myeloma or metastatic breast cancer
039	643	10.5 months (15 months)	4 and 8* mg Q3 weeks	Placebo	Metastatic prostate cancer
011	773	3.8 months (9 months)	4 and 8* mg Q3 weeks	Placebo	Metastatic solid tumor other than breast or prostate cancer

* Patients who were randomized to the 8-mg Zometa group are not included in any of the analyses in this package insert.

Table 3: Solid Tumor Patients by Cancer Type and Treatment Arm

Cancer Type	Zometa® 4 mg N	Placebo N
NSCLC	124	121
Renal	26	19
Small Cell Lung	19	22
Colorectal	19	16
Unknown	17	14
Bladder	11	16
GI (Other)	10	12
Head and Neck	6	4
Genitourinary	6	6
Malignant Melanoma	5	4
Hepatobiliary	3	4
Thyroid	2	4
Other	3	2
Sarcoma	3	3
Neuroendocrine/Carcinoid	2	3
Mesothelioma	1	0

Patients evaluable for efficacy were treated with Zometa for a median duration of 12.0 months for multiple myeloma and breast cancer, 10.5 months for prostate cancer, and 3.8 months for the other solid tumors. The studies were amended twice because of renal toxicity. The Zometa infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8-mg Zometa treatment arm were switched to 4 mg. Patients who were randomized to the Zometa 8-mg group are not included in these analyses.

Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was a SRE in the prostate cancer study only. Planned analyses included the proportion of patients with a SRE during the study (the primary endpoint) and time to the first SRE. Results for the two Zometa placebo-controlled studies are given in Table 4.

Table 4: Zometa® Compared to Placebo in Patients with Bone Metastases from Prostate Cancer or Other Solid Tumors

		I. Analysis of Proportion of Patients with a SRE[1]			II. Analysis of Time to the First SRE		
Study	Study Arm & Patient Number	Proportion	Difference[2] & 95% CI	P-value	Median (Days)	Hazard Ratio[3] & 95% CI	P-value
Prostate Cancer	Zometa 4 mg (n=214)	33%	-11% (-20%, -1%)	0.02	NR	0.67 (0.49, 0.91)	0.011
	Placebo (n=208)	44%			321		
Solid Tumors	Zometa 4 mg (n=257)	38%	-7% (-15%, 2%)	0.13	230	0.73 (0.55, 0.96)	0.023
	Placebo (n=250)	44%			163		

[1]SRE=Skeletal-Related Event
[2]Difference for the proportion of patients with a SRE of Zometa 4 mg versus placebo.
[3]Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus placebo.

In the breast cancer and myeloma trial, efficacy was determined by a non-inferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with a SRE. This analysis required an estimation of pamidronate efficacy. Historical data from 1,128 patients in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of patients with a SRE by 13.1% (95% CI=7.3%,18.9%). Results of the comparison of treatment with Zometa compared to pamidronate are given in Table 5.

Table 5: Zometa® Compared to Pamidronate in Patients with Multiple Myeloma or Bone Metastases from Breast Cancer

		I. Analysis of Proportion of Patients with a SRE[1]			II. Analysis of Time to the First SRE		
Study	Study Arm & Patient Number	Proportion	Difference[2] & 95% CI	P-value	Median (Days)	Hazard Ratio[3] & 95% CI	P-value
Multiple Myeloma & Breast Cancer	Zometa 4 mg (n=561)	44%	-2% (-7.9%, 3.7%)	0.46	373	0.92 (0.77, 1.09)	0.32
	Pamidronate 90 mg (n=555)	46%			363		

[1]SRE=Skeletal-Related Event
[2]Difference for the proportion of patients with a SRE of Zometa 4 mg versus pamidronate 90 mg.
[3]Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus pamidronate 90 mg.

INDICATIONS AND USAGE

Hypercalcemia of Malignancy

Zometa® (zoledronic acid) 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.

Multiple Myeloma and Bone Metastases of Solid Tumors

Zometa is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

CONTRAINDICATIONS

Zometa® (zoledronic acid) 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® (zoledronic acid) should not exceed 4 mg and the duration of infusion should be no less than 15 minutes. In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.

SAFETY AND PHARMACOKINETIC DATA ARE LIMITED IN PATIENTS WITH SEVERE RENAL IMPAIRMENT AND THE RISK OF RENAL DETERIORATION IS INCREASED (see ADVERSE REACTIONS, Renal Toxicity).

- **ZOMETA TREATMENT IS NOT RECOMMENDED IN PATIENTS WITH BONE METASTASES WITH SEVERE RENAL IMPAIRMENT.** In the clinical studies, patients with serum creatinine >265 μmol/L or >3.0 mg/dL were excluded and there were only eight of 564 patients treated with Zometa 4 mg by 15-minute infusion with a baseline creatinine >2 mg/dL. Limited pharmacokinetic data exists in patients with creatinine clearance <30 mL/min (see CLINICAL PHARMACOLOGY).
- **PRE-EXISTING RENAL INSUFFICIENCY AND MULTIPLE CYCLES OF ZOMETA AND OTHER BISPHOSPHONATES ARE RISK FACTORS FOR SUBSEQUENT RENAL DETERIORATION WITH ZOMETA. FACTORS PREDISPOSING TO RENAL DETERIORATION, SUCH AS DEHYDRATION OR THE USE OF OTHER NEPHROTOXIC DRUGS, SHOULD BE IDENTIFIED AND MANAGED IF POSSIBLE.**
- **ZOMETA TREATMENT IN PATIENTS WITH HYPERCALCEMIA OF MALIGNANCY WITH SEVERE RENAL IMPAIRMENT SHOULD BE CONSIDERED ONLY AFTER EVALUATING THE RISKS AND BENEFITS OF TREATMENT.** In the clinical studies, patients with serum creatinine >400 μmol/L or >4.5 mg/dL were excluded.

Patients who receive Zometa should have serum creatinine assessed prior to each treatment. Patients treated with Zometa for multiple myeloma and bone metastases of solid tumors should have the dose withheld if renal function has deteriorated. (See DOSAGE AND ADMINISTRATION.) Patients with hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk.

PREGNANCY: ZOMETA SHOULD NOT BE USED DURING PREGNANCY. Zometa may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an IV dose of 4 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations. (See PRECAUTIONS, Pregnancy Category D.)

There are no studies in pregnant women using Zometa. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

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) Injection. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Patients with hypercalcemia of malignancy 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. Zometa should be used with caution with other nephrotoxic drugs.

Renal Insufficiency

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

Studies of Zometa in the treatment of hypercalcemia of malignancy excluded patients with serum creatinine ≥400 μmol/L or ≥4.5 mg/dL. Bone metastasis trials excluded patients with serum creatinine >265 μmol/L or >3.0 mg/dL and there were only eight of 564 patients treated with Zometa 4 mg by 15-minute infusion with a baseline serum creatinine >2 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. For multiple myeloma and bone metastases of solid tumors, the use of Zometa in patients with severe renal impairment is not recommended. For hypercalcemia of malignancy, 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 treating patients for hypercalcemia presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine <400 μmol/L or <4.5 mg/dL).

Patients receiving Zometa for hypercalcemia of malignancy 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.

Upon initiation of treatment in patients with multiple myeloma or metastatic bone lesions from solid tumors, with mild-to-moderate renal impairment, lower doses of Zometa are recommended. In patients who show evidence of renal deterioration during treatment, Zometa should only be resumed when serum creatinine returns to within 10% of baseline. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

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.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).

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

Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports have been infrequent. This category of drugs includes Zometa (zoledronic acid) Injection. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Laboratory Tests

Serum creatinine should be monitored prior to each dose of Zometa. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. (See WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS.)

Drug Interactions

In vitro studies indicate that zoledronic acid is approximately 22% 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. Caution is indicated when Zometa is used with other potentially nephrotoxic drugs.

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zometa is used in combination with thalidomide.

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 genotoxic 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 pre-implantation losses and a decrease in the number of implantations and live fetuses.

Pregnancy Category D (See WARNINGS.)

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake

Zometa®
(zoledronic acid) Injection

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Description: Zometa		Rev. Date: December 2005	LD&C: ______ Date: ______
Material Group No.: • USLFLTH • • Dimensions: 17 x 15	Component No.: • 5000578 • • T2005-72	Supersedes Component No.: • 5000364 • • T2005-29	LD&C: ______ Date: ______ Engineer: ______ Date: ______
Number of Colors: 1 Black			
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of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

In female rats given 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, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (≤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.

Nursing Mothers

It is not known whether Zometa is excreted in human milk. Because many drugs are excreted in human milk, and because Zometa binds to bone long term, Zometa should not be administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Zometa in pediatric patients have not been established. Because of long-term retention in bone, Zometa should only be used in children if the potential benefit outweighs the potential risk.

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. Controlled clinical studies of Zometa in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

ADVERSE REACTIONS

Hypercalcemia of Malignancy

Adverse reactions to Zometa® (zoledronic acid) 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, flushing, 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, pruritus, 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 phosphorus, and serum magnesium observed in two clinical trials of Zometa in patients with HCM are shown in Table 6.

Table 6: Grade 3-4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, 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 (>3x Upper Limit of Normal); Grade 4 (>6x Upper 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 7 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 multicenter HCM trials. Adverse events are listed regardless of presumed causality to study drug.

Table 7: 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 multicenter 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, and metastases
Digestive System: dysphagia
Hemic and Lymphatic System: granulocytopenia, thrombocytopenia, and 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.

Multiple Myeloma and Bone Metastases of Solid Tumors

The safety analysis includes patients treated in the core and extension phases of the trials. The analysis includes the 2,042 patients treated with Zometa 4 mg, pamidronate 90 mg or placebo in the three controlled multicenter bone metastases trials, including 969 patients completing the efficacy phase of the trial, and 619 patients that continued in the safety extension phase. Only 347 patients completed the extension phases and were followed for two years (or 21 months for the other solid tumor patients). The median duration of exposure for safety analysis for Zometa 4 mg (core plus extension phases) was 12.8 months for breast cancer and multiple myeloma, 10.8 months for prostate cancer, and 4.0 months for other solid tumors.

Table 8 describes adverse events that were reported by ≥10% of patients. Adverse events are listed regardless of presumed causality to study drug.

Table 8: Percentage of Patients with Adverse Events ≥10% Reported in Three Bone Metastases Clinical Trials by Body System

	Zometa® 4 mg n (%)	**Pamidronate 90 mg n (%)**	**Placebo n (%)**
Patients Studied			
Total No. of Patients	1031 (100)	556 (100)	455 (100)
Total No. of Patients with any AE	1015 (98)	548 (99)	445 (98)
Blood and Lymphatic			
Anemia	344 (33)	175 (32)	128 (28)
Neutropenia	124 (12)	83 (15)	35 (8)
Thrombocytopenia	102 (10)	53 (10)	20 (4)
Gastrointestinal			
Nausea	476 (46)	266 (48)	171 (38)
Vomiting	333 (32)	183 (33)	122 (27)
Constipation	320 (31)	162 (29)	174 (38)
Diarrhea	249 (24)	162 (29)	83 (18)
Abdominal Pain	143 (14)	81 (15)	48 (11)
Dyspepsia	105 (10)	74 (13)	31 (7)
Stomatitis	86 (8)	65 (12)	14 (3)
Sore Throat	82 (8)	61 (11)	17 (4)
General Disorders and Administration Site			
Fatigue	398 (39)	240 (43)	130 (29)
Pyrexia	328 (32)	172 (31)	89 (20)
Weakness	252 (24)	108 (19)	114 (25)
Edema Lower Limb	215 (21)	126 (23)	84 (19)
Rigors	112 (11)	62 (11)	28 (6)
Infections			
Urinary Tract Infection	124 (12)	50 (9)	41 (9)
Upper Respiratory Tract Infection	101 (10)	82 (15)	30 (7)
Metabolism			
Anorexia	231 (22)	81 (15)	105 (23)
Weight Decreased	164 (16)	50 (9)	61 (13)
Dehydration	145 (14)	60 (11)	59 (13)
Appetite Decreased	130 (13)	48 (9)	45 (10)
Musculoskeletal			
Bone Pain	569 (55)	316 (57)	284 (62)
Myalgia	239 (23)	143 (26)	74 (16)
Arthralgia	216 (21)	131 (24)	73 (16)
Back Pain	156 (15)	106 (19)	40 (9)
Pain in Limb	143 (14)	84 (15)	52 (11)
Neoplasms			
Malignant Neoplasm Aggravated	205 (20)	97 (17)	89 (20)
Nervous			
Headache	191 (19)	149 (27)	50 (11)
Dizziness (excluding vertigo)	180 (18)	91 (16)	58 (13)
Insomnia	166 (16)	111 (20)	73 (16)
Paresthesia	149 (15)	85 (15)	35 (8)
Hypoesthesia	127 (12)	65 (12)	43 (10)
Psychiatric			
Depression	146 (14)	95 (17)	49 (11)
Anxiety	112 (11)	73 (13)	37 (8)
Confusion	74 (7)	39 (7)	47 (10)
Respiratory			
Dyspnea	282 (27)	155 (28)	107 (24)
Cough	224 (22)	129 (23)	65 (14)
Skin			
Alopecia	125 (12)	80 (14)	36 (8)
Dermatitis	114 (11)	74 (13)	38 (8)

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in three clinical trials of Zometa in patients with bone metastases are shown in Tables 9 and 10.

Table 9: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

	Grade 3					
Laboratory Parameter	**Zometa® 4 mg**		**Pamidronate 90 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Serum Creatinine[1*]	7/529	(1.3%)	4/268	(1.5%)	4/241	(1.7%)
Hypocalcemia[2]	6/973	(0.6%)	4/536	(0.7%)	0/415	—
Hypophosphatemia[3]	115/973	(11.8%)	38/537	(7.1%)	14/415	(3.4%)
Hypermagnesemia[4]	19/971	(2.0%)	2/535	(0.4%)	8/415	(1.9%)
Hypomagnesemia[5]	1/971	(0.1%)	0/535	—	1/415	(0.2%)

[1] Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)
* Serum creatinine data for all patients randomized after the 15-minute infusion amendment
[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 (>3 mEq/L); Grade 4 (>8 mEq/L)
[5] Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Table 10: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

	Grade 4					
Laboratory Parameter	**Zometa® 4 mg**		**Pamidronate 90 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Serum Creatinine[1*]	2/529	(0.4%)	1/268	(0.4%)	0/241	—
Hypocalcemia[2]	7/973	(0.7%)	3/536	(0.6%)	2/415	(0.5%)
Hypophosphatemia[3]	5/973	(0.5%)	0/537	—	1/415	(0.2%)
Hypermagnesemia[4]	0/971	—	0/535	—	2/415	(0.5%)
Hypomagnesemia[5]	2/971	(0.2%)	1/535	(0.2%)	0/415	—

[1] Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)
* Serum creatinine data for all patients randomized after the 15-minute infusion amendment
[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 (>3 mEq/L); Grade 4 (>8 mEq/L)
[5] Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Among the less frequently occurring adverse events (<15% of patients), 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.

Less common adverse events reported more often with Zometa 4 mg than pamidronate included decreased weight, which was reported in 16% of patients in the Zometa 4-mg group compared with 9% in the pamidronate group. Decreased appetite was reported in slightly more patients in the Zometa 4-mg group (13%) compared with the pamidronate (9%) and placebo (10%) groups, but the clinical significance of these small differences is not clear.

Renal Toxicity

In the bone metastases trials, renal deterioration was defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine (<1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (≥1.4 mg/dL). The following are data on the incidence of renal deterioration in patients receiving Zometa 4 mg over 15 minutes in these trials. (See Table 11.)

Table 11: Percentage of Patients with Renal Function Deterioration Who Were Randomized Following the 15-Minute Infusion Amendment

Patient Population/Baseline Creatinine				
Multiple Myeloma and Breast Cancer	**Zometa® 4 mg**		**Pamidronate 90 mg**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	27/246	(11%)	23/246	(9.3%)
Abnormal	2/26	(7.7%)	2/22	(9.1%)
Total	29/272	(10.7%)	25/268	(9.3%)
Solid Tumors	**Zometa® 4 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	17/154	(11%)	10/143	(7%)
Abnormal	1/11	(9.1%)	1/20	(5%)
Total	18/165	(10.9%)	11/163	(6.7%)
Prostate Cancer	**Zometa® 4 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	12/82	(14.6%)	8/68	(11.8%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	16/92	(17.4%)	10/78	(12.8%)

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.

Evaluation of serum creatinine is recommended prior to each cycle of therapy with Zometa. In patients receiving Zometa for multiple myeloma and bone metastases of solid tumors, who show evidence of deterioration in renal function, Zometa treatment should be withheld until serum creatinine returns to within 10% of baseline.

In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients with normal and abnormal baseline renal function, including patients treated with 4 mg infused over a 15-minute period. There have been instances of this occurring after the initial Zometa dose.

Post-Marketing Experience

Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates. The majority of the reported cases are in cancer patients attendant to a dental procedure. Osteonecrosis of the jaws has multiple well-documented risk factors including a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g., anemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged. (See PRECAUTIONS.)

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

CNS: taste disturbance, hyperesthesia, tremor; ***Special Senses:*** blurred vision; ***Gastrointestinal:*** dry mouth; ***Skin:*** increased sweating; ***Musculoskeletal:*** muscle cramps; ***Cardiovascular:*** hypertension, bradycardia, hypotension (associated with syncope or circulatory collapse primarily in patients with underlying risk factors); ***Renal:*** hematuria, proteinuria; ***Allergic Reactions:*** hypersensitivity reaction, angioneurotic edema; ***General Disorders and Administration Site:*** weight increase; ***Laboratory Abnormalities:*** hyperkalemia, hypernatremia.

Cases of uveitis and episcleritis have also been reported during post-marketing use.

OVERDOSAGE

There is no experience of acute overdose with Zometa® (zoledronic acid) 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 an open-label study of zoledronic acid 4 mg in breast cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with non-Hodgkin's lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 100U/L, each value unknown). The outcome of this case is not known.

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.) In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.**

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) 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).

Multiple Myeloma and Metastatic Bone Lesions From Solid Tumors

The recommended dose of Zometa in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance >60 mL/min is 4 mg infused over no less than 15 minutes every three to four weeks. The optimal duration of therapy is not known.

Upon treatment initiation, the recommended Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are listed in the following table. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula. (See CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency.)

Baseline Creatinine Clearance (mL/min)	**Zometa® Recommended Dose***
> 60	4.0 mg
50 - 60	3.5 mg
40 - 49	3.3 mg
30 - 39	3.0 mg

*Doses calculated assuming target AUC of 0.66(mg•hr/L) (CrCl=75 mL/min)

During treatment, serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dL
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL

In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zometa should be re-initiated at the same dose as that prior to treatment interruption.

Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

Preparation of Solution

4-mg Dose: Vials of Zometa concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Reduced Doses for Patients with Baseline CrCl ≤60 mL/min: Withdraw an appropriate volume of the 5 mL - Zometa concentrate as needed:

4.4 mL for 3.5 mg dose
4.1 mL for 3.3 mg dose
3.8 mL for 3.0 mg dose

The withdrawn concentrate must be 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 dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2°C-8°C (36°F-46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between 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.) In the trials and in post-marketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.**

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 5-mL vial contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP, water for injection and 24 mg of sodium citrate, USP.

Carton of 1 vial . . . . .NDC 0078-0387-25

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

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NOVARTIS

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