CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-223

FINAL PRINTED LABELING

Zometa®

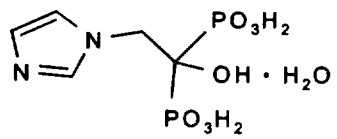
(zoledronic acid for injection)
For Intravenous Infusion

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.

Pharmacokinetics

Distribution

Single 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa® (zoledronic acid for injection) were given to 32 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process, showing population half-lives of $t_{½\alpha}$ 0.23 hours and $t_{½\beta}$ 1.75 hours for the early distribution and elimination of the drug, and a terminal elimination half-life $t_{½\gamma}$ of 167 hours describing the low concentrations in plasma observed up to 28 days post dose.

In vitro studies of zoledronic acid showed no affinity for the cellular components of human blood. Binding to human plasma proteins was low (approximately 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.

Excretion

In a study in patients with cancer and bone metastases (n=32), 44 ± 18% of the administered zoledronic acid dose was recovered in the urine within 24 hours. The balance, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed 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 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 not affected by body weight, body mass index, or gender. In a study in patients with cancer, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=3) to 15 minutes (n=4) resulted in a 30% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 393 ± 100 ng/mL vs 267 ± 41 ng/mL) and a 21% increase in the total AUC (412 ± 107 ng/mL vs 496 ± 212 ng/mL).

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 years to 85 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: 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).

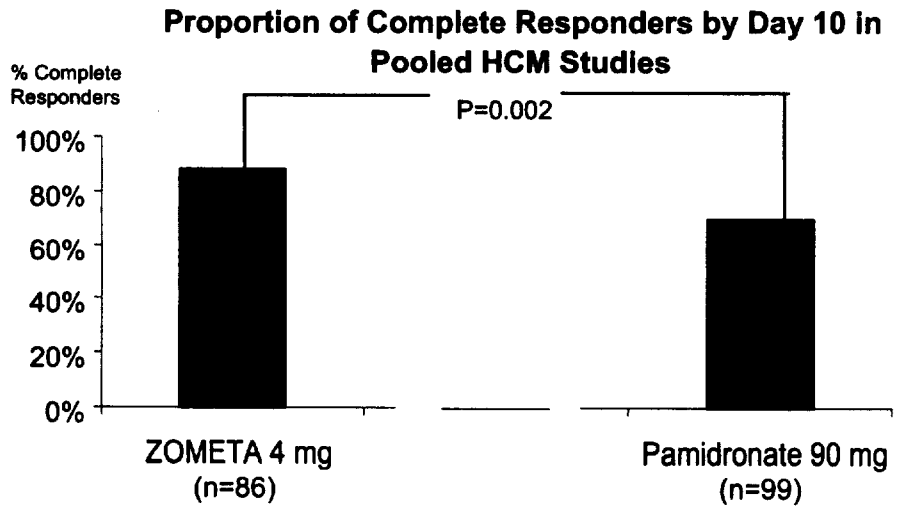
Clinical Trials

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). **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



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

INDICATIONS AND USAGE

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.

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. 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)

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.

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 occure, 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 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 $\geq$ 400 µmol/L or $\geq$ 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.)

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% bound to plasma proteins. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. 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.

ADVERSE REACTIONS

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 2.

Table 2: 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 3 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 3: 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.

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

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* $\geq$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).

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-223

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-223

SEP 21 2000

Novartis Pharmaceuticals Corporation
Attention: Ms. Ellen Cutler
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Cutler:

Please refer to your new drug application (NDA) dated December 21, 1999, received December 21, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid for injection).

We acknowledge receipt of your submissions dated January 7, February 2, 11, and 28, March 21, April 7, 13, 14(2), 19, 20, 27, and 28, May 5, 10, 11, 12(2), 17, 18, 26, and 31, June 1, 2, and 9, August 8, 14, 18, and 22, and September 8, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however it will be necessary for you to address the following:

The information submitted provides convincing evidence that zoledronate is effective in the treatment of tumor-induced hypercalcemia. However, data from ongoing trials indicate that zoledronate use may be associated with an increased risk for renal injury. Preliminary analyses suggest that this risk may be related to dose, duration of use, length of infusion, patient age, and baseline renal function.

Completion of ongoing studies will allow for a more comprehensive evaluation of zoledronate's renal safety profile, including an assessment of the effect of the recently implemented protocol amendments.

In order to address this outstanding safety concern, you must provide the complete study reports for clinical trials 010, 011 and 039. You must also provide updated proposed labeling for the use of zoledronate in the treatment of tumor-induced hypercalcemia. The updated proposed labeling must address and/or incorporate any changes warranted by this further information including repeat dosing recommendations, proposed infusion time instructions, and any suggested requirements for renal surveillance.

Also, revisions of the draft labeling submitted on August 11, 2000, may be required after we have reviewed the additional material, or if additional information relating to the safety or effectiveness of this drug becomes available. Please also contact the Division of Metabolic and Endocrine Drug Products regarding clarification of financial disclosure information submitted in the original NDA.

Your complete response to this letter should include a safety update as described in 21 CFR 314.50(d)(5)(vi)(*b*). Please provide updated information as listed below. The update should cover all studies, both U.S. and foreign and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major

amendment nor will the review clock be reactivated until all deficiencies have been addressed. The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/ for 9/21/00

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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ON ORIGINAL

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