

Report from the FDA

Approval Summary for Zoledronic Acid for Treatment of Multiple Myeloma and Cancer Bone Metastases

Amna Ibrahim,¹ Nancy Scher, Grant Williams, Rajeshwari Sridhara, Ning Li, Gang Chen, John Leighton, Brian Booth, Jogarao V. S. Gobburu, Atiqur Rahman, Yung Hsieh, Rebecca Wood, Debra Vause, and Richard Pazdur

Division of Oncology Drug Products, Center for Drug Evaluation and Research, Rockville, Maryland 20857

Abstract

Purpose: This article summarizes data submitted to the United States Food and Drug Administration for marketing approval of zoledronic acid (Zol; Novartis Pharmaceuticals, East Hanover, NJ), a bisphosphonate drug for treating patients with bone metastases.

Experimental Design: We review the chemistry, toxicology, pharmacology, and clinical study results submitted to support the supplemental New Drug Application for Zol for treatment of patients with bone metastases. Four- and 8-mg Zol doses were selected for Phase III trials based on bone resorption markers and clinical efficacy parameters. Patients with bone metastases were randomized in three Phase III studies (prostate cancer, solid tumors, and multiple myeloma or breast cancer) to receive 4 or 8 mg of Zol or to a control arm. The control was a placebo in the prostate cancer study and the other solid tumor study and was 90 mg of pamidronate (Pam) in the study of breast cancer and multiple myeloma. Studies were amended twice because of renal toxicity, initially to increase Zol infusion time from 5 to 15 min and later to decrease the dose in the Zol 8-mg arm to 4 mg. The efficacy end point was skeletal-related events (SREs), a composite end point consisting of pathologic fracture, radiation therapy to bone, changes in antineoplastic therapy for bone pain (prostate cancer only), surgery to bone, or spinal cord compression. This end point was analyzed either as the proportion of patients with SRE or time to first SRE. The breast cancer and myeloma study used a noninferiority statistical analysis methods to determine efficacy.

Results: In prostate cancer, both the proportions analysis and time-to-SRE analysis showed significantly less bone

morbidity on Zol (4 mg) than placebo, but no significant difference between Zol (8 mg) and placebo in either analysis. In the solid tumor study, the time to SRE analysis but not the proportions analysis showed significantly less skeletal morbidity on Zol (4 mg) than placebo, and Zol (8 mg) was significantly better than placebo in both analyses. The breast cancer and myeloma study demonstrated noninferiority of Zol compared with Pam, with Zol retaining at least 49.3% of the Pam treatment effect previously demonstrated in placebo-controlled trials. Zol was approved on February 22, 2002, by the United States Food and Drug Administration for the “treatment of patients with multiple myeloma and 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.” The recommended dose and schedule is 4 mg of Zol infused over 15 min every 3–4 weeks. Increased Zol doses and shorter infusions are not recommended because of potential renal toxicity.

Introduction

Bone metastases are found at autopsy in at least 25% of cancer patients, most frequently in lung, breast, and kidney carcinomas (73, 32, and 25%, respectively) and occur universally in multiple myeloma (1). Bone metastases are classified according to radiographic appearance as osteolytic or osteoblastic. In preclinical models, the osteoclast, a cell important in bone remodeling, plays a role in bone morbidity in both types of lesions by secreting enzymes that erode bone (2). Skeletal complications, including pain, pathologic fracture, and spinal cord compression, are managed locally with surgery or radiotherapy or systemically with chemotherapy and analgesics.

Zol² is a bisphosphonate drug previously granted marketing approval for treatment of malignant hypercalcemia of malignancy in August 2001. Bisphosphonates are hydrolysis-resistant PP₁ derivatives that have a high affinity for bone and inhibit osteoclastic bone resorption (3). FDA has approved several bisphosphonates for treatment of hypercalcemia of malignancy, osteoporosis, or cancer bone metastases. Pam (Aredia; Novartis Pharmaceuticals, East Hanover, NJ) was previously the only bisphosphonate approved for treating bone metastases; the Pam-marketing approval was limited to treatment of multiple myeloma and breast cancer osteolytic bone lesions (4–8).

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¹ To whom requests for reprints should be addressed, at Division of Oncology Drug Products, Center for Drug Evaluation and Research, 5600 Fisher's Lane, HFD-150, Rockville, MD 20857. Phone: (301) 594-2473; Fax: (301) 594-0499; E-mail: ibrahima@cder.fda.gov.

² The abbreviations used are: Zol, zoledronic acid; FDA, Food and Drug Administration; Pam, Pamidronate; SRE, skeletal-related event; SMR, skeletal morbidity rate; CI, confidence interval; ODAC, Oncologic Drugs Advisory Committee; NDA, New Drug Application.

Table 1 Placebo-controlled studies in prostate cancer and other solid tumors

Study	Study arm	Proportion of patients with SRE			Time to first SRE		
		Proportion	Difference and 95% CI	P	Median time to first SRE	HR ^a 95% CI	P
Prostate cancer study	Zol (4 mg)	33%	-11 (-20, -2)	0.021	NR	0.67 (0.49, 0.91)	0.011
	Zol (8 mg)	38%	-6 (-15, 4)	0.22	363	0.91 (0.68, 1.23)	0.54
	Placebo	44%			321		
Solid tumors study	Zol (4 mg)	38%	-7 (-15, 2)	0.13	230	0.73 (0.55, 0.96)	0.023
	Zol (8 mg)	35%	-9 (-18, -1)	0.023	219	0.74 (0.56, 0.98)	0.035
	Placebo	44%			163		

^a HR, hazard ratio *versus* placebo.

Previous Bisphosphonate Approvals for Bone Metastases

The Pam studies demonstrate that bisphosphonates can provide clinical benefit in patients with bone metastases. The Pam NDA approval provides a regulatory precedent for this drug class. The design, details, and results of the Pam trials provide the critical basis for the applicant's noninferiority trial comparing Zol to Pam in breast cancer and myeloma.

FDA involvement in the design and review of these trials established the regulatory precedent that a composite end point, a SRE, represented an adequate efficacy measure for new drug approval and that a decrease in SREs represented clinical benefit. Each of the elements (pathologic fractures, radiation to bone lesions, surgery to bone, and spinal cord compression) composing the end point represented an adequate morbidity measure. The FDA did not allow hypercalcemic episodes as SRE elements. These events are not local irreversible events as are other elements of the end point, and physicians effectively treat hypercalcemia with bisphosphonates.

The first Pam NDA approval was based on a single 9-month placebo-controlled study in multiple myeloma. The second Pam application was for breast cancer and included two 12-month placebo-controlled studies, one in patients receiving chemotherapy and a second in patients receiving hormonal therapy. Subsequent Pam approvals increased the labeled treatment duration from 1 to 2 years and decreased the infusion duration for treatment of patients with bone metastases from breast cancer from 4 to 2 h.

Early Pam protocols emphasized the SMR. The SMR is calculated by dividing the sum of all events by time on study. The SMR is not optimal for efficacy evaluation because the analysis does not differentiate between multiple events occurring in an individual patient *versus* single events occurring in multiple patients. The calculation of a rate makes the false assumption that events occur at a fixed rate over time. Subsequently, FDA has emphasized end points of proportions of patients with a SRE and time to first SRE. The two end points are closely related: both use only the first SRE in a patient. Of the two, FDA has suggested that the time to first SRE may provide a more precise estimate of treatment effect.

Chemistry

The active ingredient of Zometa is Zol monohydrate, chemically designated as (1-hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate. The molecular formula

is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ with a molecular weight of 290.11. Zol, a bisphosphonic acid derivative, is prepared by a multistep synthesis and isolated as a monohydrate. It is an odorless, white crystalline material. It is soluble at alkaline pH and sparingly soluble in water. The drug product is supplied as a sterile, lyophilized powder in 4-mg strength (on an anhydrous basis) intended for reconstitution before i.v. infusion. The recommended storage temperature is 25°C.

Toxicology

Toxicology studies indicated no significant effects on central nervous system function, gastrointestinal motility, muscle contraction, respiration, hemodynamic parameters, or cardiac conduction. The principal organs affected by Zol parenteral administration were the kidney, bone, gastrointestinal system, liver, spleen, lung, adrenal gland, and thymus. Injection site irritation was observed. Zol was not genotoxic in standard assays.

Zol was teratogenic in rats as evidenced by increased external, visceral, and skeletal malformations. No teratogenicity was observed in rabbits. Findings in rat reproductive toxicity studies were skeletal malformations and an increase in pre- and postimplantation losses. The reproductive toxicity findings with bisphosphonates are likely to be related to their common therapeutic mechanism, *i.e.*, sequestration of calcium and inhibition of bone resorption. Bisphosphonates lower maternal blood plasma calcium and sequester in maternal bone where they prevent the release of calcium by binding with hydroxyapatite and via their action on osteoclasts to prevent bone resorption. Bisphosphonate effects on osteoclasts via modulation of the mevalonate pathway are a possible, although not the only mechanism. Developing fetal bone is adversely affected because it does not get the calcium it needs from the mother and may be directly affected as bisphosphonates readily cross the placental barrier and are taken up in the developing fetal skeleton, thus interfering with growth. General effects such as maternal and fetal toxicity, dystocia, and effects on fertility (pre- and postimplantation losses) may be attributable to the decreased plasma calcium with possible effects even on cell growth and differentiation because calcium is a needed ingredient. At this time, there are no data available from human studies regarding risk to the fetus of bisphosphonate use during pregnancy, however, based on information described above, Zol has been classified as pregnancy category D and should not be used during pregnancy.

Table 2 Active control study in myeloma and breast cancer

Study arm	Proportion of patients with SRE			Time to first SRE		
	Proportion	Difference and 95% CI	P	Time to first SRE (HR) ^a	95% CI	P
Zol (4 mg)	44%	-2 (-7.9, 3.7)	0.46	0.92	(0.77, 1.09)	0.31
Zol (8 mg)	46%	0 (-6.1, 5.8)	0.96	0.99	(0.83, 1.18)	0.91
Pamidronate (90 mg)	46%					

^a HR, hazard ratio *versus* placebo.

Clinical Pharmacology

The pharmacokinetics of Zol were characterized by a three compartment model. The distribution half-life (α - $t_{1/2}$) was 14 min, followed by a β -phase of 1.9 h. A prolonged terminal phase, with a half-life of at least 146 h, may indicate a slow release of Zol from the bone back into the plasma. Zol pharmacokinetics were dose proportional from 2 to 16 mg based on C_{max} and area under the curve ($AUC_{24 h}$). Zol dosed every 21 days did not demonstrate significant plasma accumulation. *In vitro* studies indicated that 22% of Zol is protein bound.

The excretion of Zol is primarily renal. Approximately 40% of the radiolabeled Zol dose was recovered in urine within 24 h. Only traces of Zol were observed in the urine after day 2, suggesting a prolonged period of Zol binding to bone. Population modeling described the Zol clearance as a function of creatinine clearance. On the basis of a comparison of $AUC_{24 h}$, patients with mild or moderate renal impairment had 15 and 43% higher exposure, respectively, than patients with normal renal function. However, no significant relationship between Zol exposure (AUC) and adverse events could be established. The use of Zol in patients with severe renal failure is not recommended.

The effect of hepatic impairment on pharmacokinetics was not studied. *In vitro* studies showed no inhibition of or metabolism by cytochrome P-450 enzymes, but no *in vivo* drug-drug interaction studies were submitted.

Dose-finding Studies

Doses selected for clinical trials were based on changes in bone resorption markers (including serum COOH-terminal telopeptide and urinary N-telopeptide/creatinine ratio) and preliminary evidence of efficacy. In initial studies of patients with cancer bone metastases, single 0.1–0.4-mg Zol doses caused minimal change in markers. Markers were consistently suppressed for at least 4 weeks at doses \geq 4 mg. In a study of patients with multiple myeloma or breast cancer bone metastases, 280 patients were randomized to receive Aredia (90 mg) or Zol doses of 0.4, 2, or 4 mg and were evaluated for the incidence of SREs. Analyses suggested a significant difference between the SRE rate in the 4- and 0.4-mg groups. On the basis of the results of these studies, Zol doses of 4 and 8 mg were selected for Phase III evaluation.

Phase III Clinical Studies

Safety and efficacy of 4 mg of Zol and 8 mg of Zol were evaluated in patients with cancer bone metastases in three randomized studies. A combined study in breast cancer and mul-

tle myeloma used an active control, 90 mg of Pam. Separate studies in solid tumors and prostate cancer used a placebo control. In all studies, documented bone metastases were required at entry. Study duration was 13, 9, and 15 months for the breast cancer/myeloma, solid tumor, and prostate cancer studies, respectively.

Because of renal toxicity early in the studies, the Zol infusion duration was increased from 5 to 15 min. After accrual was complete for all studies, but although many patients were still receiving study medication, the 8-mg dose was discontinued because of continued renal toxicity. Patients on the Zol 8-mg arms were given 4-mg Zol doses until study completion. Statistical plans were amended to exclude the 8-mg arms from the primary analysis before the analysis of the study.

In each study, the primary analysis was specified as a comparison of proportion of patients having at least one SRE (the proportions analysis). Change in chemotherapy because of increased pain was an SRE in the prostate cancer study only.

Efficacy Results

Efficacy results are summarized in Tables 1 and 2.

Myeloma and Breast Cancer Study

Myeloma and breast cancer were evaluated in an international, multicenter, double-blind study that randomized patients 1:1:1 to 4 mg of Zol, 8 mg of Zol, or 90 mg of Pam i.v. every 3–4 weeks for 12 months. Randomization was stratified by three disease strata: myeloma; breast cancer hormonal treatment; and breast cancer chemotherapy treatment. The primary analysis was a noninferiority analysis of the proportion of patients with at least one SRE, performed after 13 months (12 months of treatment and 1 month of follow-up).

Results from the 1648 randomized patients demonstrated that 4 mg of Zol are effective in decreasing the skeletal morbidity of myeloma and of breast cancer metastatic to bone. This conclusion was based on a noninferiority analysis demonstrating that 4 mg of Zol retained at least 50% of the Pam treatment effect previously demonstrated in placebo-controlled studies. Efficacy determination in noninferiority studies involves both a statistical comparison of study drug (4 mg of Zol) to a concurrent active control (90 mg of Pam) and an inference that had the active control been replaced by a placebo, 4 mg of Zol would have demonstrated superiority to the placebo. This judgment involves a comparison between the historical placebo-controlled trials and the current active-controlled trial.

The FDA used a two 95% CI method of analysis. The first step was to estimate the size of the Pam treatment effect based

Table 3 Solid tumor patients by cancer type

Cancer type	Zol (4 mg) (n)	Placebo (n)	Zol (8 mg) (n)
Non-small cell lung cancer	124	121	130
Renal	26	19	28
Small cell lung cancer	19	22	21
Colorectal	19	16	17
Unknown	17	14	16
Bladder	11	16	6
GI (other)	10	12	7
Head and neck	6	4	6
Genitourinary	6	6	3
Malignant melanoma	5	4	6
Hepatobiliary	3	4	4
Thyroid	2	4	5
Other	3	2	4
Sarcoma	3	3	3
Neuroendocrine/carcinoid	2	3	2
Non-Hodgkin's lymphoma	0	0	3
Mesothelioma	1	0	1

on historical data. The combined data from the three Pam trials showed that 52.0% of patients receiving placebo compared with 38.9% receiving Pam had a SRE. Thus, the treatment effect was 13.1% (95% CI: 7.3, 18.9). This method used the lower limit of the confidence interval as the conservative estimate of Pam effect size (7.3%). Next, it estimated the fraction of this Pam effect that is retained by Zol (with 95% confidence). On the Zol 4-mg arm of this noninferiority trial, 44% of patients had at least one SRE compared with 46% on the Pam arm, a difference of -2% (95% CI: -7.9, 3.7). The upper bound of the 95% CI excludes Zol being 3.7% worse than Pam. The following are the calculations estimating that at least 49.3% of the Pam-*versus*-placebo effect has been retained: $(7.3 - 3.7\%) / 7.3\% = 49.3\%$. This method is conservative because it twice uses the 95% confidence interval, first to estimate the historical effect size and then to estimate the current effect size. Even using this conservative methodology, efficacy of Zol is adequately demonstrated.

The ODAC voted (yes, 11; no, 0) that these trials provided substantial evidence of Zol 4-mg efficacy in breast cancer and multiple myeloma.

Solid Tumor Study The solid tumor study entered 773 patients with solid cancers metastatic to bone (Table 3). Randomization was stratified according to cancer type as either non-small cell lung cancer or other tumors. However, the stratification was imperfect, and conclusions could not be made based on these subgroups. In the proportions analysis, the Zol 4-mg arm showed a nonsignificant trend when compared with placebo (38 *versus* 44%, respectively, $P = 0.13$), whereas the Zol 8-mg arm was significantly better than placebo (35 *versus* 44%, respectively, $P = 0.023$). Time-to-first-SRE analysis showed a significant benefit for both the Zol 4-mg arm and the Zol 8-mg arm compared with placebo (Table 1). There was an improvement by ~2 months in time-to-first-SRE in the 4-mg treatment arm.

An important regulatory consideration was whether these study results could be extrapolated to all solid tumors. The positive efficacy findings for both Zol arms of the other solid tumor study provide support that Zol has a beneficial effect on

bone metastases from many different types of primary tumors. Evidence of Zol activity from other NDA trials in both blastic and lytic metastases provide additional support.

The ODAC voted (yes, 10; no, 0) that the other solid tumor study represented substantial evidence of Zol 4-mg efficacy in patients with solid tumors metastatic to bone.

Prostate Cancer Study

The prostate cancer study entered patients with disease progressing after at least one hormonal therapy, documented by three consecutive increasing PSAs. Six hundred forty-three patients were randomized to one of three arms. Efficacy analyses demonstrated significantly less skeletal morbidity on the Zol 4-mg arm than on the placebo arm both by the proportions analysis (33 *versus* 44%, respectively, $P = 0.021$) and time-to-first-SRE analysis ($P = 0.011$). A trend in favor of Zol 8 mg arm compared with placebo was noted, but the difference was not statistically significant (Table 1). Multivariate analyses, including covariates of treatment arm, prior skeletal events, time from initial diagnosis of cancer to bone metastases, time from first bone metastases to randomization, \log_e of baseline PSA, and baseline analgesic scores, demonstrated no statistically significant difference between results in the Zol 8-mg arm and placebo.

The lack of supportive evidence provided by efficacy analyses of Zol 80-mg *versus* placebo and the lack of previous experience with bisphosphonates in osteoblastic bone metastases were concerns to the FDA reviewers. The FDA review team found no good explanation for the nonpositive finding for Zol 8-mg compared with placebo. Bias was not likely because patients remained blinded to treatment assignment before and after the amendment decreasing Zol dose from 8 to 4 mg. Differences in study conduct were not apparent. Drug doses and follow-up visits were similar on the three arms of the study. It seems unlikely that the higher dose of 8 mg is less efficacious than a dose of 4 mg. There are no preclinical or clinical data suggesting less bone effects with higher dose. A potential explanation for the nonpositive Zol 8-mg finding is chance. For these NDA studies with 80% statistical power, we expect a false-negative finding one of five times. This NDA had three trials, each with two different Zol doses, leading to six Zol-*versus*-placebo comparisons. At least one nonpositive comparison is likely.

Osteoclast activation appears to be an important underlying mechanism for causing bone destruction and hence bone morbidity from both osteolytic and osteoblastic metastases (2). Zol suppresses laboratory markers of bone resorption in patients with osteoblastic as well as in osteolytic disease. Therefore, the therapeutic effects of Zol documented in osteolytic disease was viewed as potentially supportive evidence of Zol effectiveness in osteoblastic disease.

ODAC voted (yes, 11; no, 0) that evidence of Zol efficacy in patients with lytic metastases should be considered supportive of Zol efficacy in prostate cancer. ODAC then voted (yes, 10; no, 1) that the Zol 4-mg NDA trials collectively represent substantial evidence of efficacy in prostate cancer.

Table 4 Incidence of renal function deterioration^a in patients receiving the 4 mg of Zol infused over 15 min

A. Multiple myeloma and breast cancer				
Baseline creatinine	Zol (4 mg)		Pam (90 mg)	
	n/N	(%)	n/N	(%)
Normal	23/246	(9.3%)	20/246	(8.1%)
Abnormal	1/26	(3.8%)	2/22	(9.1%)
Total	24/272	(8.8%)	22/268	(8.2%)
B. Solid Tumors				
Baseline creatinine	Zol (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%)
C. Prostate Cancer				
Baseline creatinine	Zol (4 mg)		Placebo	
	n/N	(%)	n/N	(%)
Normal	10/82	(12.2%)	7/68	(10.3%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	14/92	(15.2%)	9/78	(11.5%)

^a Renal deterioration is increase of 0.5 mg/dl for normal baseline creatinine (<1.4 mg/dl) or increase of 1.0 mg/dl for abnormal baseline creatinine (≥mg/dl).

Safety Results

Renal toxicity was the only serious safety finding after Zol treatment. Renal toxicity was related to dose (more with 8 than 4 mg), infusion duration (more with infusion over 5 than 15 min), and total number of infusions. Table 4 compares the incidence of renal deterioration in patients receiving 4 mg of Zol to patients receiving placebo or Pam. The risk of renal deterioration with 4 mg of Zol was greater than placebo but similar to Pam. Most instances were mild and reversible, with rare episodes of acute renal failure. Renal dialysis was required by 30 of 2873 patients who participated in the three randomized trials. The majority (23 of 30) of these patients had multiple myeloma or prostate cancer, diseases associated with renal dysfunction.

Four mg of Zol must be infused over at least 15 min, and clinical monitoring of serum creatinine is recommended before each dose. In clinical trials, 4 mg of Zol were held for renal deterioration until the creatinine returned to within 10% of baseline. Caution is indicated for patients with elevated baseline creatinine. There are no data in patients with severe renal impairment as clinical studies excluded patients with creatinine > 3.0 mg/dl. The study population did not have extensive concomitant exposure to other nephrotoxic drugs.

Findings associated with other bisphosphonates such as arthralgias, pyrexia, electrolyte disturbances, and hypocalcemia were noted for 4 mg of Zol and 90 mg of Pam but did not necessitate treatment discontinuation. Anemia was slightly more common with 4 mg of Zol, compared with placebo.

Regulatory Issues

Compelling evidence is presented in Tables 1 and 2 that 4 mg of Zol are effective in patients with bone metastases from tumors that commonly metastasize to bone. In both of the placebo-controlled studies, the time to SRE analyses of 4 mg of Zol were strongly supportive ($P = 0.011$ for prostate cancer and $P = 0.023$ for solid tumors). Although the Zol 8-mg arm was not significantly better than placebo in the prostate cancer study, CIs did not rule out an important benefit (lower bound of CI of the hazard ratio of 0.67). The efficacy data did not show a consistent dose-response effect. Results appeared better for 4 mg of Zol than 8 mg of Zol in the prostate cancer study, but this finding was not observed in either the solid tumor or breast cancer/myeloma study. A noninferiority study comparing 4 mg of Zol to 90 mg of Pam in over 1600 patients convincingly demonstrated Zol 4-mg efficacy in multiple myeloma and breast cancer.

These efficacy results are mutually supportive and provide substantial evidence of efficacy for Zol treatment of patients with bone metastases. On the basis of these considerations, the ODAC voted (yes, 11; no, 0) that the FDA should approve 4 mg of Zol for treatment of patients with multiple myeloma and bone metastases from all solid tumors irrespective of the primary tumor.

Current and past bisphosphonate approvals based on evaluation of bone morbidity highlight a common misconception that an improvement in survival is required for FDA cancer drug approval (9). The SRE end points supporting bisphosphonate approvals represent only one of several nonsurvival end points that have supported cancer drug-marketing approval. Over two-thirds of cancer drug approvals in the past 12 years were based on nonsurvival end points (10).

The end points and study designs supporting marketing approval of the bisphosphonates Pam and Zol may provide a useful paradigm for development of selected cancer drugs. Bisphosphonates differ from traditional cytotoxic drugs: they are less toxic, and their intended target is the osteoclast, not the cancer cell. The lesser toxicity allows a blinded, placebo-controlled trial, which minimizes bias in evaluation of the symptom-driven composite end point. The noncancer target of therapy, the osteoclast, allows continuation of study drug after tumor progression and after change in anticancer therapy.

Approval and Phase IV Postmarketing Commitments

Zol (Zometa; Novartis Pharmaceuticals) was approved by the FDA on February 22, 2002, for the "treatment of patients with multiple myeloma and 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." The recommended dose and schedule is 4 mg infused over 15 min every 3–4 weeks. The NDA applicant made two postmarketing commitments to perform Phase IV trials. The first was to conduct a pharmacokinetic and safety study in patients with renal dysfunction and serum creatinine > 3 mg/dl. The second commitment was to conduct a drug-drug interaction study to evaluate the effect of thalido-

mide on the pharmacokinetics and safety of Zometa in patients with multiple myeloma.

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