

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20036/S024**

**APPROVAL LETTER**



NDA 20-036/S-024

Novartis Pharmaceuticals Corporation  
Attention: Robert A Miranda  
Associate Director, Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

Dear Mr. Miranda:

We acknowledge receipt on August 13, 2001, of your supplemental drug application dated August 13, 2001, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Aredia (pamidronate disodium injection).

This supplemental application proposes to change the administration rate for the infusion of Aredia from 24 hours to 2 to 24 hours. This change applies to the indication for the treatment of moderate and severe hypercalcemia of malignancy, with or without bone metastases.

We also acknowledge receipt of your submission dated August 16, 2001, providing revised draft labeling.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 16, 2001) with the following change. Please remove the phrase, "60 mg/10mL," from the first sentence of the *Reconstitution* subsection of the **DOSAGE AND ADMINISTRATION** section.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-036/S-024." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20036/S024**

**APPROVED DRAFT LABELING**

8/16/01



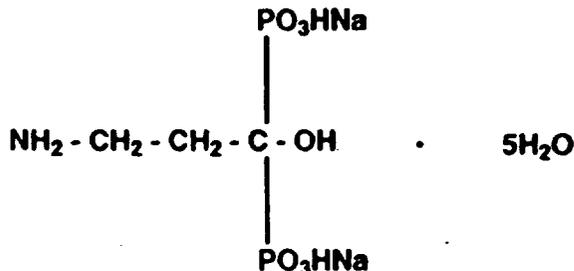
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Aredia®  
pamidronate disodium for injection  
For Intravenous Infusion  
Rx only  
Prescribing Information



**DESCRIPTION**

Aredia, pamidronate disodium (APD), is a bone-resorption inhibitor available in 30-mg or 90-mg vials for intravenous administration. Each 30-mg, and 90-mg vial contains, respectively, 30 mg and 90 mg of sterile, lyophilized pamidronate disodium and 470 mg and 375 mg of mannitol, USP. The pH of a 1% solution of pamidronate disodium in distilled water is approximately 8.3. Aredia, a member of the group of chemical compounds known as bisphosphonates, is an analog of pyrophosphate. Pamidronate disodium is designated chemically as phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, pentahydrate, (APD), and its structural formula is



Pamidronate disodium is a white-to-practically-white powder. It is soluble in water and in 2N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is C<sub>3</sub>H<sub>9</sub>NO<sub>7</sub>P<sub>2</sub>Na<sub>2</sub>•5H<sub>2</sub>O and its molecular weight is 369.1.

*Inactive Ingredients.* Mannitol, USP, and phosphoric acid (for adjustment to pH 6.5 prior to lyophilization).

**CLINICAL PHARMACOLOGY**

The principal pharmacologic action of Aredia is inhibition of bone resorption. Although the mechanism of antiresorptive action is not completely understood, several factors are thought to contribute to this action. Aredia adsorbs to calcium phosphate (hydroxyapatite) crystals in bone and may directly block dissolution of this mineral component of bone. In vitro studies also suggest that inhibition of osteoclast activity contributes to inhibition of bone resorption. In animal studies, at doses recommended for the treatment of hypercalcemia, Aredia inhibits bone resorption apparently without inhibiting bone formation and mineralization. Of relevance to the treatment of hypercalcemia of malignancy is the finding that Aredia inhibits the accelerated bone resorption that results from osteoclast hyperactivity induced by various tumors in animal studies.

**Pharmacokinetics**

Cancer patients (n=24) who had minimal or no bony involvement were given an intravenous infusion of 30, 60, or 90 mg of Aredia over 4 hours and 90 mg of Aredia over 24 hours (Table 1).

**Distribution**

The mean ± SD body retention of pamidronate was calculated to be 54 ± 16% of the dose over 120 hours.

**Metabolism**

Pamidronate is not metabolized and is exclusively eliminated by renal excretion.

### **Excretion**

After administration of 30, 60, and 90 mg of Aredia over 4 hours, and 90 mg of Aredia over 24 hours, an overall mean  $\pm$  SD of  $46 \pm 16\%$  of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean  $\pm$  SD elimination half-life is  $28 \pm 7$  hours. Mean  $\pm$  SD total and renal clearances of pamidronate were  $107 \pm 50$  mL/min and  $49 \pm 28$  mL/min, respectively. The rate of elimination from bone has not been determined.

### **Special Populations**

There are no data available on the effects of age, gender, or race on the pharmacokinetics of pamidronate.

#### **Pediatric**

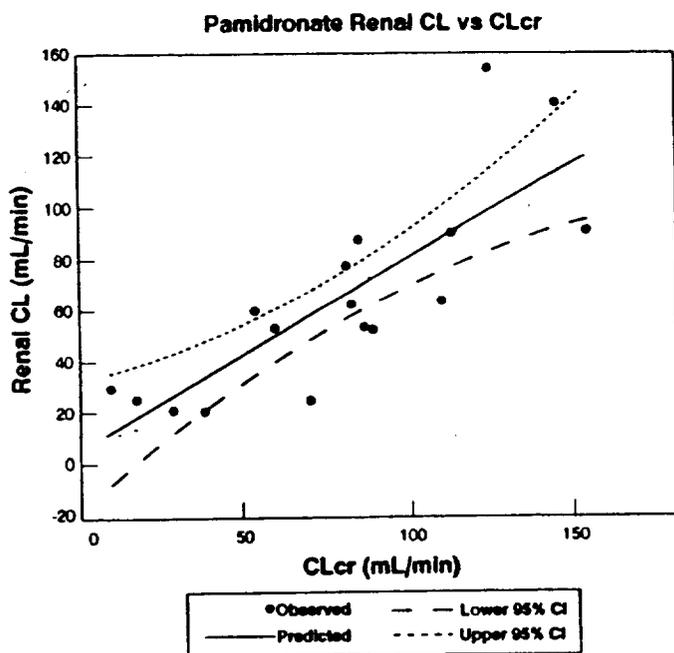
Pamidronate is not labeled for use in the pediatric population.

#### **Renal Insufficiency**

The pharmacokinetics of pamidronate were studied in cancer patients (n=19) with normal and varying degrees of renal impairment. Each patient received a single 90-mg dose of Aredia infused over 4 hours. The renal clearance of pamidronate in patients was found to closely correlate with creatinine clearance (see Figure 1). A trend toward a lower percentage of drug excreted unchanged in urine was observed in renally impaired patients. Adverse experiences noted were not found to be related to changes in renal clearance of pamidronate. Given the recommended dose, 90 mg infused over 4 hours, excessive accumulation of pamidronate in renally impaired patients is not anticipated if Aredia is administered on a monthly basis.

**Figure 1: Pamidronate renal clearance as a function of creatinine clearance in patients with normal and impaired renal function.**

The lines are the mean prediction line and 95% confidence intervals.



#### **Hepatic Insufficiency**

There are no human pharmacokinetic data for Aredia in patients who have hepatic insufficiency.

#### **Drug-Drug Interactions**

There are no human pharmacokinetic data for drug interactions with Aredia.

**Table 1**  
**Mean (SD, CV%) Pamidronate Pharmacokinetic Parameters in Cancer Patients**  
**(n=6 for each group)**

<u>Maximum Dose (infusion rate)</u>	<u>Percent Concentration (<math>\mu\text{g/mL}</math>)</u>	<u>Total of dose excreted in urine</u>	<u>Renal Clearance (<math>\text{mL/min}</math>)</u>	<u>Clearance (<math>\text{mL/min}</math>)</u>
30 mg (4 hrs)	0.73 (0.14, 19.1%)	43.9 (14.0, 31.9%)	136 (44, 32.4%)	58 (27, 46.5%)
60 mg (4 hrs)	1.44 (0.57, 39.6%)	47.4 (47.4, 54.4%)	88 (56, 63.6%)	42 (28, 66.7%)
90 mg (4 hrs)	2.61 (0.74, 28.3%)	45.3 (25.8, 56.9%)	103 (37, 35.9%)	44 (16, 36.4%)
90 mg (24 hrs)	1.38 (1.97, 142.7%)	47.5 (10.2, 21.5%)	101 (58, 57.4%)	52 (42, 80.8%)

After intravenous administration of radiolabeled pamidronate in rats, approximately 50%-60% of the compound was rapidly adsorbed by bone and slowly eliminated from the body by the kidneys. In rats given 10 mg/kg bolus injections of radiolabeled Aredia, approximately 30% of the compound was found in the liver shortly after administration and was then redistributed to bone or eliminated by the kidneys over 24-48 hours. Studies in rats injected with radiolabeled Aredia showed that the compound was rapidly cleared from the circulation and taken up mainly by bones, liver, spleen, teeth, and tracheal cartilage. Radioactivity was eliminated from most soft tissues within 1-4 days; was detectable in liver and spleen for 1 and 3 months, respectively; and remained high in bones, trachea, and teeth for 6 months after dosing. Bone uptake occurred preferentially in areas of high bone turnover. The terminal phase of elimination half-life in bone was estimated to be approximately 300 days.

#### **Pharmacodynamics**

Serum phosphate levels have been noted to decrease after administration of Aredia, presumably because of decreased release of phosphate from bone and increased renal excretion as parathyroid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return toward normal. Phosphate therapy was administered in 30% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned toward normal within 7-10 days.

Urinary calcium/creatinine and urinary hydroxyproline/creatinine ratios decrease and usually return to within or below normal after treatment with Aredia. These changes occur within the first week after treatment, as do decreases in serum calcium levels, and are consistent with an antiresorptive pharmacologic action.

#### **Hypercalcemia of Malignancy**

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in metastatic bone disease and hypercalcemia of malignancy. 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. Correction of excessive bone resorption and adequate fluid administration to correct volume deficits are therefore essential to the management of hypercalcemia.

Most cases of hypercalcemia associated with malignancy occur in patients who have breast cancer; squamous-cell tumors of the lung or head and neck; renal-cell carcinoma; and certain hematologic malignancies, such as multiple myeloma and some types of lymphomas. A few less-common malignancies, including vasoactive intestinal-peptide-producing tumors and cholangiocarcinoma, have a high incidence of

hypercalcemia as a metabolic complication. Patients who have hypercalcemia of malignancy can generally be divided into two groups, according to the pathophysiologic mechanism involved.

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 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*

In one double-blind clinical trial, 52 patients who had hypercalcemia of malignancy were enrolled to receive 30 mg, 60 mg, or 90 mg of Aredia as a single 24-hour intravenous infusion if their corrected serum calcium levels were  $\geq 12.0$  mg/dL after 48 hours of saline hydration.

The mean baseline-corrected serum calcium for the 30-mg, 60-mg, and 90-mg groups were 13.8 mg/dL, 13.8 mg/dL, and 13.3 mg/dL, respectively.

The majority of patients (64%) had decreases in albumin-corrected serum calcium levels by 24 hours after initiation of treatment. Mean-corrected serum calcium levels at days 2-7 after initiation of treatment with Aredia were significantly reduced from baseline in all three dosage groups. As a result, by 7 days after initiation of treatment with Aredia, 40%, 61%, and 100% of the patients receiving 30 mg, 60 mg, and 90 mg of Aredia, respectively, had normal-corrected serum calcium levels. Many patients (33%-53%) in the 60-mg and 90-mg dosage groups continued to have normal-corrected serum calcium levels, or a partial response ( $\geq 15\%$  decrease of corrected serum calcium from baseline), at day 14.

In a second double-blind, controlled clinical trial, 65 cancer patients who had corrected serum calcium levels of  $\geq 12.0$  mg/dL after at least 24 hours of saline hydration were randomized to receive either 60 mg of Aredia as a single 24-hour intravenous infusion or 7.5 mg/kg of Didronel (etidronate disodium) as a 2-hour intravenous infusion daily for 3 days. Thirty patients were randomized to receive Aredia and 35 to receive Didronel.

The mean baseline-corrected serum calcium for the Aredia 60-mg and Didronel groups were 14.6 mg/dL and 13.8 mg/dL, respectively.

By day 7, 70% of the patients in the Aredia group and 41% of the patients in the Didronel group had normal-corrected serum calcium levels ( $P < 0.05$ ). When partial responders ( $\geq 15\%$  decrease of serum calcium from baseline) were also included, the response rates were 97% for the Aredia group and 65% for the Didronel group ( $P < 0.01$ ). Mean-corrected serum calcium for the Aredia and Didronel groups decreased from baseline values to 10.4 and 11.2 mg/dL, respectively, on day 7. At day 14, 43% of patients in the Aredia group and 18% of patients in the Didronel group still had normal-corrected serum calcium levels, or maintenance of a partial response. For responders in the Aredia and Didronel groups, the median duration of response was similar (7 and 5 days, respectively). The time course of effect on corrected serum calcium is summarized in the following table.

### **Change in Corrected Serum Calcium by Time from Initiation of Treatment**

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)	P-Value <sup>1</sup>	
Baseline	14.6	13.8	
24	-0.3	-0.5	
48	-1.5	-1.1	
72	-2.6	-2.0	
96	-3.5	-2.0	<0.01
168	-4.1	-2.5	<0.01

<sup>1</sup> Comparison between treatment groups

In a third multicenter, randomized, parallel double-blind trial, a group of 69 cancer patients with hypercalcemia was enrolled to receive 60 mg of Aredia as a 4- or 24-hour infusion, which was compared to a saline treatment group. Patients who had a corrected serum calcium level of  $\geq 12.0$  mg/dL after 24 hours of saline hydration were eligible for this trial.

The mean baseline-corrected serum calcium levels for Aredia 60-mg 4-hour infusion, Aredia 60-mg 24-hour infusion, and saline infusion were 14.2 mg/dL, 13.7 mg/dL, and 13.7 mg/dL, respectively.

By day 7 after initiation of treatment, 78%, 61%, and 22% of the patients had normal-corrected serum calcium levels for the 60-mg 4-hour infusion, 60-mg 24-hour infusion, and saline infusion, respectively. At day 14, 39% of the patients in the Aredia 60-mg 4-hour infusion group and 26% of the patients in the Aredia 60-mg 24-hour infusion group had normal-corrected serum calcium levels or maintenance of a partial response.

For responders, the median duration of complete responses was 4 days and 6.5 days for Aredia 60-mg 4-hour infusion and Aredia 60-mg 24-hour infusion, respectively.

In all three trials, patients treated with Aredia had similar response rates in the presence or absence of bone metastases. Concomitant administration of furosemide did not affect response rates.

Thirty-two patients who had recurrent or refractory hypercalcemia of malignancy were given a second course of 60 mg of Aredia over a 4- or 24-hour period. Of these, 41% showed a complete response and 16% showed a partial response to the retreatment, and these responders had about a 3-mg/dL fall in mean-corrected serum calcium levels 7 days after retreatment.

In a fourth multicenter, randomized, double-blind trial, 103 patients with cancer and hypercalcemia (corrected serum calcium > 12.0 mg/dl) received 90 mg of Aredia as a 2-hour infusion. The mean baseline corrected serum calcium was 14.0 mg/dl. Patients were not required to receive IV hydration prior to drug administration, but all subjects did receive at least 500 ml of IV saline hydration concomitantly with the pamidronate infusion. By day 10 after drug infusion, 70% of patients had normal corrected serum calcium levels (< 10.8 mg/dl).

Unlike Aredia 60 mg, the drug has not been investigated in a controlled clinical trial employing a 90 mg dose infused over a 4 hour period. (a 1995 paper compared 90 mg of pamidronate over 4 hours to elodronate in patients with HCM — would therefore delete this sentence.)

### Paget's Disease

Paget's disease of bone (osteitis deformans) is an idiopathic disease characterized by chronic, focal areas of bone destruction complicated by concurrent excessive bone repair, affecting one or more bones. These changes result in thickened but weakened bones that may fracture or bend under stress. Signs and

symptoms may be bone pain, deformity, fractures, neurological disorders resulting from cranial and spinal nerve entrapment and from spinal cord and brain stem compression, increased cardiac output to the involved bone, increased serum alkaline phosphatase levels (reflecting increased bone formation) and/or urine hydroxyproline excretion (reflecting increased bone resorption).

### **Clinical Trials**

In one double-blind clinical trial, 64 patients with moderate to severe Paget's disease of bone were enrolled to receive 5 mg, 15 mg, or 30 mg of Aredia as a single 4-hour infusion on 3 consecutive days, for total doses of 15 mg, 45 mg, and 90 mg of Aredia.

The mean baseline serum alkaline phosphatase levels were 1409 U/L, 983 U/L, and 1085 U/L, and the mean baseline urine hydroxyproline/creatinine ratios were 0.25, 0.19, and 0.19 for the 15-mg, 45-mg, and 90-mg groups, respectively.

The effects of Aredia on serum alkaline phosphatase (SAP) and urine hydroxy-proline/creatinine ratios (UOHP/C) are summarized in the following table:

### **Percent of Patients With Significant % Decreases in SAP and UOHP/C**

SAP	UOHP/C					
<u>% Decrease</u>	<u>15 mg</u>	<u>45 mg</u>	<u>90 mg</u>	<u>15 mg</u>	<u>45 mg</u>	<u>90 mg</u>
≥50	26	33	60	15	47	72
≥30	40	65	83	35	57	85

The median maximum percent decreases from baseline in serum alkaline phosphatase and urine hydroxyproline/creatinine ratios were 25%, 41%, and 57%, and 25%, 47%, and 61% for the 15-mg, 45-mg, and 90-mg groups, respectively. The median time to response (≥50% decrease) for serum alkaline phosphatase was approximately 1 month for the 90-mg group, and the response duration ranged from 1 to 372 days.

No statistically significant differences between treatment groups, or statistically significant changes from baseline were observed for the bone pain response, mobility, and global evaluation in the 45-mg and 90-mg groups. Improvement in radiologic lesions occurred in some patients in the 90-mg group.

Twenty-five patients who had Paget's disease were retreated with 90 mg of Aredia. Of these, 44% had a ≥50% decrease in serum alkaline phosphatase from baseline after treatment, and 39% had a ≥50% decrease in urine hydroxyproline/creatinine ratio from baseline after treatment.

### **Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma**

Osteolytic bone metastases commonly occur in patients with multiple myeloma or breast cancer. These cancers demonstrate a phenomenon known as osteotropism, meaning they possess an extraordinary affinity for bone. The distribution of osteolytic bone metastases in these cancers is predominantly in the axial skeleton, particularly the spine, pelvis, and ribs, rather than the appendicular skeleton, although lesions in the proximal femur and humerus are not uncommon. This distribution is similar to the red bone marrow in which slow blood flow possibly assists attachment of metastatic cells. The surface-to-volume ratio of trabecular bone is much higher than cortical bone, and therefore disease processes tend to occur more floridly in trabecular bone than at sites of cortical tissue.

These bone changes can result in patients having evidence of osteolytic skeletal destruction leading to severe bone pain that requires either radiation therapy or narcotic analgesics (or both) for symptomatic relief. These changes also cause pathologic fractures of bone in both the axial and appendicular skeleton. Axial skeletal fractures of the vertebral bodies may lead to spinal cord compression or vertebral body

collapse with significant neurologic complications. Also, patients may experience episode(s) of hypercalcemia.

### ***Clinical Trials***

In a double-blind, randomized, placebo-controlled trial, 392 patients with advanced multiple myeloma were enrolled to receive Aredia or placebo in addition to their underlying antimyeloma therapy to determine the effect of Aredia on the occurrence of skeletal-related events (SREs). SREs were defined as episodes of pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression. Patients received either 90 mg of Aredia or placebo as a monthly 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for efficacy (196 Aredia, 181 placebo). The proportion of patients developing any SRE was significantly smaller in the Aredia group (24% vs 41%,  $P < 0.001$ ), and the mean skeletal morbidity rate (#SRE/year) was significantly smaller for Aredia patients than for placebo patients (mean: 1.1 vs 2.1,  $P < .02$ ). The times to the first SRE occurrence, pathologic fracture, and radiation to bone were significantly longer in the Aredia group ( $P = .001$ ,  $.006$ , and  $.046$ , respectively). Moreover, fewer Aredia patients suffered any pathologic fracture (17% vs 30%,  $P = .004$ ) or needed radiation to bone (14% vs 22%,  $P = .049$ ).

In addition, decreases in pain scores from baseline occurred at the last measurement for those Aredia patients with pain at baseline ( $P = .026$ ) but not in the placebo group. At the last measurement, a worsening from baseline was observed in the placebo group for the Spitzer quality of life variable ( $P < .001$ ) and ECOG performance status ( $P < .011$ ) while there was no significant deterioration from baseline in these parameters observed in Aredia-treated patients.\*

After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the Aredia group than the placebo group ( $P = .015$ ). In addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for Aredia patients vs placebo patients ( $P = .008$ ), and time to first SRE was significantly longer in the Aredia group compared to placebo ( $P = .016$ ). Fewer Aredia patients suffered vertebral pathologic fractures (16% vs 27%,  $P = .005$ ). Survival of all patients was not different between treatment groups.

Two double-blind, randomized, placebo-controlled trials compared the safety and efficacy of 90 mg of Aredia infused over 2 hours every 3 to 4 weeks for 24 months to that of placebo in preventing SREs in breast cancer patients with osteolytic bone metastases who had one or more predominantly lytic metastases of at least 1 cm in diameter: one in patients being treated with antineoplastic chemotherapy and the second in patients being treated with hormonal antineoplastic therapy at trial entry.

382 patients receiving chemotherapy were randomized, 185 to Aredia and 197 to placebo. 372 patients receiving hormonal therapy were randomized, 182 to Aredia and 190 to placebo. All but three patients were evaluable for efficacy. Patients were followed for 24 months of therapy or until patients went off study. Median duration of follow-up was 13 months in patients receiving chemotherapy and 17 months in patients receiving hormone therapy. Twenty five percent of the patients in the chemotherapy study and 37% of the patients in the hormone therapy study received Aredia for 24 months. The efficacy results are shown in the table below:

N	Breast Cancer Patients Receiving Chemotherapy						Breast Cancer Patients Receiving Hormonal Therapy					
	Any SRE		Radiation		Fractures		Any SRE		Radiation		Fractures	
	A	P	A	P	A	P	A	P	A	P	A	P
5	18	195	185	195	185	195	182	189	182	189	182	189
Skeletal Morbidity Rate (#SRE/Year)												
Mean	2.5	3.7	0.8	1.3	1.6	2.2	2.4	3.6	0.6	1.2	1.6	2.2
P-Value	<.001		<.001†		.018†		.021		.013†		.040†	
Proportion of Patients having an SRE												
	46	65%	28	45	36	49	55	63	31%	40	45	55
	%		%	%	%	%	%	%		%	%	%
P-Value	<.001		<.001†		.014†		.094		.058†		.054†	
Median Time to SRE (months)												
	13.	7.0	NR*	14.2	25.	13.	10.	7.4	NR**	23.	20.	12.
	9		*		8	3	9			4	6	8
P-Value	<.001		<.001†		.009†		.118		.016†		.113†	

†Fractures and radiation to bone were two of several secondary endpoints. The statistical significance of these analyses may be overestimated since numerous analyses were performed.

\*\*NR = Not Reached

Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 months. The complete + partial response rate was 33% in Aredia patients and 18% in placebo patients treated with chemotherapy (P=.001). No difference was seen between Aredia and placebo in hormonally-treated patients.

Pain and analgesic scores, ECOG performance status and Spitzer quality of life index were measured at baseline and periodically during the trials. The changes from baseline to the last measurement carried forward are shown in the table below:

#### Mean Change ( $\Delta$ ) from Baseline at Last Measurement

	Breast Cancer Patients Receiving Chemotherapy					Breast Cancer Patients Receiving Hormonal Therapy				
	Aredia		Placebo		A vs P	Aredia		Placebo		A vs P
	N	Mean <sup>Δ</sup>	N	Mean <sup>Δ</sup>	P-Value*	N	Mean <sup>Δ</sup>	N	Mean <sup>Δ</sup>	P-Value*
Pain Score	175	+0.93	18 3	+1.69	.050	17 3	+0.50	17 9	+1.60	.007
Analgesic Score	175	+0.74	18 3	+1.55	.009	17 3	+0.90	17 9	+2.28	<.001
ECOG PS	178	+0.81	18 6	+1.19	.002	17 5	+0.95	18 2	+0.90	.773
Spitzer QOL	177	-1.76	18	-2.21	.103	17	-1.86	18	-2.05	.409

Decreases in pain, analgesic scores and ECOG PS, and increases in Spitzer QOL indicate an improvement from baseline.

\*The statistical significance of analyses of these secondary endpoints of pain, quality of life, and performance status in all three trials may be overestimated since numerous analyses were performed.

#### **INDICATIONS AND USAGE**

##### **Hypercalcemia of Malignancy**

Aredia, in conjunction with adequate hydration, is indicated for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases. Patients who have either epidermoid or non-epidermoid tumors respond to treatment with Aredia. 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 Aredia in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

##### **Paget's Disease**

Aredia is indicated for the treatment of patients with moderate to severe Paget's disease of bone. The effectiveness of Aredia was demonstrated primarily in patients with serum alkaline phosphatase  $\geq 3$  times the upper limit of normal. Aredia therapy in patients with Paget's disease has been effective in reducing serum alkaline phosphatase and urinary hydroxyproline levels by  $\geq 50\%$  in at least 50% of patients, and by  $\geq 30\%$  in at least 80% of patients. Aredia therapy has also been effective in reducing these biochemical markers in patients with Paget's disease who failed to respond, or no longer responded to other treatments.

##### **Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma**

Aredia is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. The Aredia treatment effect appeared to be smaller in the study of breast cancer patients receiving hormonal therapy than in the study of those receiving chemotherapy, however, overall evidence of clinical benefit has been demonstrated (see CLINICAL PHARMACOLOGY, Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma, Clinical Trials section.)

#### **CONTRAINDICATIONS**

Aredia is contraindicated in patients with clinically significant hypersensitivity to Aredia or other bisphosphonates.

#### **WARNINGS**

In both rats and dogs, nephropathy has been associated with intravenous (bolus and infusion) administration of Aredia.

Two 7-day intravenous infusion studies were conducted in the dog wherein Aredia was given for 1, 4, or 24 hours at doses of 1-20 mg/kg for up to 7 days. In the first study, the compound was well tolerated at 3 mg/kg (1.7 x highest recommended human dose [HRHD] for a single intravenous infusion) when administered for 4 or 24 hours, but renal findings such as elevated BUN and creatinine levels and renal tubular necrosis occurred when 3 mg/kg was infused for 1 hour and at doses of  $\geq 10$  mg/kg. In the second study, slight renal tubular necrosis was observed in 1 male at 1 mg/kg when infused for 4 hours. Additional findings included elevated BUN levels in several treated animals and renal tubular dilation and/or inflammation at  $\geq 1$  mg/kg after each infusion time.

Aredia was given to rats at doses of 2, 6, and 20 mg/kg and to dogs at doses of 2, 4, 6, and 20 mg/kg as a 1-hour infusion, once a week, for 3 months followed by a 1-month recovery period. In rats, nephrotoxicity

was observed at  $\geq 6$  mg/kg and included increased BUN and creatinine levels and tubular degeneration and necrosis. These findings were still present at 20 mg/kg at the end of the recovery period. In dogs, moribundity/death and renal toxicity occurred at 20 mg/kg as did kidney findings of elevated BUN and creatinine levels at  $\geq 6$  mg/kg and renal tubular degeneration at  $\geq 4$  mg/kg. The kidney changes were partially reversible at 6 mg/kg. In both studies, the dose level that produced no adverse renal effects was considered to be 2 mg/kg (1.1 x HRHD for a single intravenous infusion).

Patients who receive an intravenous infusion of Aredia should have periodic evaluations of standard laboratory and clinical parameters of renal function.

Studies conducted in young rats have reported the disruption of dental dentine formation following single- and multi-dose administration of bisphosphonates. The clinical significance of these findings is unknown.

## **PRECAUTIONS**

### **General**

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium, and potassium, should be carefully monitored following initiation of therapy with Aredia. Cases of asymptomatic hypophosphatemia (12%), hypokalemia (7%), hypomagnesemia (11%), and hypocalcemia (5%-12%), were reported in Aredia-treated patients. Rare cases of symptomatic hypocalcemia (including tetany) have been reported in association with Aredia therapy. If hypocalcemia occurs, short-term calcium therapy may be necessary. In Paget's disease of bone, 17% of patients treated with 90 mg of Aredia showed serum calcium levels below 8 mg/dL.

Aredia has not been tested in patients who have class Dc renal impairment (creatinine  $>5.0$  mg/dL), and in a few multiple myeloma patients with serum creatinine  $\geq 3.0$  mg/dL. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics.) Clinical judgment should determine whether the potential benefit outweighs the potential risk in such patients.

### **Laboratory Tests**

Serum calcium, electrolytes, phosphate, magnesium and creatinine, and CBC, differential, and hematocrit/hemoglobin must be closely monitored in patients treated with Aredia. Patients who have preexisting anemia, leukopenia, or thrombocytopenia should be monitored carefully in the first 2 weeks following treatment.

### **Drug Interactions**

Concomitant administration of a loop diuretic had no effect on the calcium-lowering action of Aredia.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 104-week carcinogenicity study (daily oral administration) in rats, there was a positive dose response relationship for benign adrenal pheochromocytoma in males ( $P < 0.00001$ ). Although this condition was also observed in females, the incidence was not statistically significant. When the dose calculations were adjusted to account for the limited oral bioavailability of Aredia in rats, the lowest daily dose associated with adrenal pheochromocytoma was similar to the intended clinical dose. Adrenal pheochromocytoma was also observed in low numbers in the control animals and is considered a relatively common spontaneous neoplasm in the rat. Aredia (daily oral administration) was not carcinogenic in an 80-week study in mice.

Aredia was nonmutagenic in six mutagenicity assays: Ames test, Salmonella and Escherichia/liver-microsome test, nucleus-anomaly test, sister-chromatid-exchange study, point-mutation test, and micronucleus test in the rat.

In rats, decreased fertility occurred in first-generation offspring of parents who had received 150 mg/kg of Aredia orally; however, this occurred only when animals were mated with members of the same dose group. Aredia has not been administered intravenously in such a study.

### **Pregnancy Category C**

There are no adequate and well-controlled studies in pregnant women.

Bolus intravenous studies conducted in rats and rabbits determined that Aredia produces maternal toxicity and embryo/fetal effects when given during organogenesis at doses of 0.6 to 8.3 times the highest

recommended human dose for a single intravenous infusion. As it has been shown that Aredia can cross the placenta in rats and has produced marked maternal and nonteratogenic embryo/fetal effects in rats and rabbits, it should not be given to women during pregnancy.

#### **Nursing Mothers**

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

#### **Pediatric Use**

Safety and effectiveness of Aredia in pediatric patients have not been established.

### **ADVERSE REACTIONS**

#### **Clinical Studies**

##### ***Hypercalcemia of Malignancy***

Transient mild elevation of temperature by at least 1°C was noted 24 to 48 hours after administration of Aredia in 34% of patients in clinical trials. In the saline trial, 18% of patients had a temperature elevation of at least 1°C 24 to 48 hours after treatment.

Drug-related local soft-tissue symptoms (redness, swelling or induration and pain on palpation) at the site of catheter insertion were most common (18%) in patients treated with 90 mg of Aredia. ~~When all on-therapy events are considered, that rate rises to 41%.~~ Symptomatic treatment resulted in rapid resolution in all patients.

Rare cases of uveitis, iritis, scleritis, and episcleritis have been reported, including one case of scleritis, and one case of uveitis upon separate rechallenges.

~~Four of 128~~ Five of 231 patients (32%) who received Aredia during the three ~~four~~ U.S. controlled hypercalcemia clinical studies were reported to have had seizures, 2 of whom had preexisting seizure disorders. None of the seizures were considered to be drug-related by the investigators. However, a possible relationship between the drug and the occurrence of seizures cannot be ruled out. It should be noted that in the saline arm 1 patient (4%) had a seizure. ~~(this paragraph should reflect the 90 mg 2-hour data— if no seizures reported than can remain as is.)~~

There are no controlled clinical trials comparing the efficacy and safety of 90 mg Aredia over 24 hours to 2 hours in patients with hypercalcemia of malignancy. However, a comparison of data from separate clinical trials suggests that the overall safety profile in patients who received 90 mg Aredia<sup>®</sup> over 24 hours is similar to those who received 90 mg Aredia over 2 hours. The only notable differences observed were an increase in the proportion of patients in the Aredia<sup>®</sup> 24 hour group who experienced fluid overload and electrolyte/mineral abnormalities."

At least 15% of patients treated with Aredia for hypercalcemia of malignancy also experienced the following adverse events during a clinical trial:

*General:* Fluid overload, generalized pain

*Cardiovascular:* Hypertension

*Gastrointestinal:* Abdominal pain, anorexia, constipation, nausea, vomiting

*Genitourinary:* Urinary tract infection

*Musculoskeletal:* Bone pain

*Laboratory abnormality:* Anemia, hypokalemia, hypomagnesemia, hypophosphatemia

Many of these adverse experiences may have been related to the underlying disease state.

The following table lists the adverse experiences considered to be treatment-related during comparative, controlled U.S. trials.

#### **Treatment-Related Adverse Experiences Reported in Three U.S. Controlled**

**Clinical Trials**Percent of Patients

<u>Aredia</u>	<u>Didronel</u>		<u>Saline</u>		
60 mg	60 mg	90 mg	7.5 mg/kg		
<u>over 4 hr</u>	<u>over 24 hr</u>	<u>over 24 hr</u>	<u>x 3 days</u>		
n=23	n=73	n=17	n=35	n=23	
<b>General</b>					
Edema	0	1	0	0	0
Fatigue	0	0	12	0	0
Fever	26	19	18	9	0
Fluid overload	0	0	0	6	0
Infusion-site reaction	0	4	18	0	0
Moniliasis	0	0	6	0	0
Rigors	0	0	0	0	4
<b>Gastrointestinal</b>					
Abdominal pain	0	1	0	0	0
Anorexia	4	1	12	0	0
Constipation	4	0	6	3	0
Diarrhea	0	1	0	0	0
Dyspepsia	4	0	0	0	0
<b>Gastrointestinal</b>					
hemorrhage	0	0	6	0	0
Nausea	4	0	18	6	0
Stomatitis	0	1	0	3	0
Vomiting	4	0	0	0	0
<b>Respiratory</b>					
Dyspnea	0	0	0	3	0
Rales	0	0	6	0	0
Rhinitis	0	0	6	0	0
<b>Upper respiratory</b>					
infection	0	3	0	0	0
<b>CNS</b>					
Anxiety	0	0	0	0	4
Convulsions	0	0	0	3	0
Insomnia	0	1	0	0	0
Nervousness	0	0	0	0	4
Psychosis	4	0	0	0	0
Somnolence	0	1	6	0	0
Taste perversion	0	0	0	3	0
<b>Cardiovascular</b>					
Atrial fibrillation	0	0	6	0	4
Atrial flutter	0	1	0	0	0

Cardiac failure	0	1	0	0	0
Hypertension	0	0	6	0	4
Syncope	0	0	6	0	0
Tachycardia	0	0	6	0	4
<b>Endocrine</b>					
Hypothyroidism	0	0	6	0	0
<b>Hemic and Lymphatic</b>					
Anemia	0	0	6	0	0
Leukopenia	4	0	0	0	0
Neutropenia	0	1	0	0	0
Thrombocytopenia	0	1	0	0	0
<b>Musculoskeletal</b>					
Myalgia	0	1	0	0	0
<b>Urogenital</b>					
Uremia	4	0	0	0	0
<b>Laboratory Abnormalities</b>					
Hypocalcemia	0	1	12	0	0
Hypokalemia	4	4	18	0	0
Hypomagnesemia	4	10	12	3	4
Hypophosphatemia	0	9	18	3	0
Abnormal liver function	0	0	0	3	0
<b>Paget's Disease</b>					

Transient mild elevation of temperature  $>1^{\circ}\text{C}$  above pretreatment baseline was noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of Aredia in clinical trials.

Drug-related musculoskeletal pain and nervous system symptoms (dizziness, headache, paresthesia, increased sweating) were more common in patients with Paget's disease treated with 90 mg of Aredia than in patients with hypercalcemia of malignancy treated with the same dose.

Adverse experiences considered to be related to trial drug, which occurred in at least 5% of patients with Paget's disease treated with 90 mg of Aredia in two U.S. clinical trials, were fever, nausea, back pain, and bone pain.

At least 10% of all Aredia-treated patients with Paget's disease also experienced the following adverse experiences during clinical trials:

*Cardiovascular:* Hypertension

*Musculoskeletal:* Arthrosis, bone pain

*Nervous system:* Headache

Most of these adverse experiences may have been related to the underlying disease state.

#### **Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma**

The most commonly reported ( $>15\%$ ) adverse experiences occurred with similar frequencies in the Aredia and placebo treatment groups, and most of these adverse experiences may have been related to the underlying disease state or cancer therapy.

#### **Commonly Reported Adverse Experiences in Three U.S. Controlled Clinical Trials**

	Aredia 90 mg over 4 hours N=205 %	Placebo N=187 %	Aredia 90 mg over 2 hours N=367 %	Placebo N=386 %	All Aredia 90 mg N=572 %	Placebo N=573 %
<b>General</b>						
Asthenia	16.1	17.1	25.6	19.2	22.2	18.5
Fatigue	31.7	28.3	40.3	28.8	37.2	29.0
Fever	38.5	38.0	38.1	32.1	38.5	34.0
Metastases	1.0	3.0	31.3	24.4	20.5	17.5
Pain	13.2	11.8	15.0	18.1	14.3	16.1
<b>Digestive System</b>						
Anorexia	17.1	17.1	31.1	24.9	26.0	22.3
Constipation	28.3	31.7	36.0	38.6	33.2	35.1
Diarrhea	26.8	26.8	29.4	30.6	28.5	29.7
Dyspepsia	17.6	13.4	18.3	15.0	22.6	17.5
Nausea	35.6	37.4	63.5	59.1	53.5	51.8
Pain Abdominal	19.5	16.0	24.3	18.1	22.6	17.5
Vomiting	16.6	19.8	46.3	39.1	35.7	32.8
<b>Hemic and Lymphatic</b>						
Anemia	47.8	41.7	39.5	36.8	42.5	38.4
Granulocytopenia	20.5	15.5	19.3	20.5	19.8	18.8
Thrombocytopenia	16.6	17.1	12.5	14.0	14.0	15.0
<b>Musculo-skeletal System</b>						
Arthralgias	10.7	7.0	15.3	12.7	13.6	10.8
Myalgia	25.4	15.0	26.4	22.5	26.0	20.1
Skeletal Pain	61.0	71.7	70.0	75.4	66.8	74.0
<b>CNS</b>						
Anxiety	7.8	9.1	18.0	16.8	14.3	14.3
Headache	24.4	19.8	27.2	23.6	26.2	22.3
Insomnia	17.1	17.2	25.1	19.4	22.2	19.0
<b>Respiratory System</b>						
Coughing	26.3	22.5	25.3	19.7	25.7	20.6
Dyspnea	22.0	21.4	35.1	24.4	30.4	23.4
Pleural Effusion	2.9	4.3	15.0	9.1	10.7	7.5
Sinusitis	14.6	16.6	16.1	10.4	15.6	12.0
Upper Resp. Tract Infection	32.2	28.3	19.6	20.2	24.1	22.9
<b>Urogenital System</b>						
Urinary tract Infection	15.6	9.1	20.2	17.6	18.5	15.6

Of the toxicities commonly associated with chemotherapy, the frequency of vomiting, anorexia, and anemia were slightly more common in the Aredia patients whereas stomatitis and alopecia occurred at a frequency

similar to that in placebo patients. In the breast cancer trials, mild elevations of serum creatinine occurred in 18.5% of Aredia patients and 12.3% of placebo patients. Mineral and electrolyte disturbances, including hypocalcemia, were reported rarely and in similar percentages of Aredia-treated patients compared with those in the placebo group. The reported frequencies of hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia for Aredia-treated patients were 3.3%, 10.5%, 1.7%, and 4.4%, respectively, and for placebo-treated patients were 1.2%, 12%, 1.7%, and 4.5%, respectively. In previous hypercalcemia of malignancy trials, patients treated with Aredia (60 or 90 mg over 24 hours) developed electrolyte abnormalities more frequently (see ADVERSE REACTIONS, Hypercalcemia of Malignancy).

Arthralgias and myalgias were reported slightly more frequently in the Aredia group than in the placebo group (13.6% and 26% vs 10.8% and 20.1%, respectively).

In multiple myeloma patients, there were five Aredia-related serious and unexpected adverse experiences. Four of these were reported during the 12-month extension of the multiple myeloma trial. Three of the reports were of worsening renal function developing in patients with progressive multiple myeloma or multiple myeloma-associated amyloidosis. The fourth report was the adult respiratory distress syndrome developing in a patient recovering from pneumonia and acute gangrenous cholecystitis. One Aredia-treated patient experienced an allergic reaction characterized by swollen and itchy eyes, runny nose, and scratchy throat within 24 hours after the sixth infusion.

In the breast cancer trials, there were four Aredia-related adverse experiences, all moderate in severity, that caused a patient to discontinue participation in the trial. One was due to interstitial pneumonitis, another to malaise and dyspnea. One Aredia patient discontinued the trial due to a symptomatic hypocalcemia. Another Aredia patient discontinued therapy due to severe bone pain after each infusion, which the investigator felt was trial-drug-related.

### Post-Marketing Experience

Rare instances of allergic manifestations have been reported, including hypotension, dyspnea, or angioedema, and, very rarely, anaphylactic shock. Aredia is contraindicated in patients with clinically significant hypersensitivity to Aredia or other bisphosphonates (see CONTRAINDICATIONS).

### OVERDOSAGE

There have been several cases of drug maladministration of intravenous Aredia in hypercalcemia patients with total doses of 225 mg to 300 mg given over 2 1/2 to 4 days. All of these patients survived, but they experienced hypocalcemia that required intravenous and/or oral administration of calcium.

In addition, one obese woman (95 kg) who was treated with 285 mg of Aredia/day for 3 days experienced high fever (39.5°C), hypotension (from 170/90 mmHg to 90/60 mmHg), and transient taste perversion, noted about 6 hours after the first infusion. The fever and hypotension were rapidly corrected with steroids.

If overdosage occurs, symptomatic hypocalcemia could also result; such patients should be treated with short-term intravenous calcium.

### DOSAGE AND ADMINISTRATION

#### Hypercalcemia of Malignancy

Consideration should be given to the severity of as well as the symptoms of hypercalcemia. Vigorous saline hydration alone may be sufficient for treating mild, asymptomatic hypercalcemia. Overhydration should be avoided in patients who have potential for cardiac failure. In hypercalcemia associated with hematologic malignancies, the use of glucocorticoid therapy may be helpful.

#### Moderate Hypercalcemia

**The recommended dose of Aredia in moderate hypercalcemia (corrected serum calcium\* of approximately 12-13.5 mg/dL) is 60 to 90 mg given as a SINGLE DOSE, intravenous infusion over 2 to 24 hours. -Longer infusions (i.e., > 2 hours) may reduce the risk for renal toxicity, particularly in patients with pre-existing renal insufficiency. The 60-mg dose is given as an initial, SINGLE DOSE, intravenous infusion over at least 4 hours. The 90-mg dose must be given by an initial, SINGLE-**

~~DOSE, intravenous infusion over 24 hours. For select patients 90 mg can be infused over 2 to 24 hours.~~

#### **Severe Hypercalcemia**

The recommended dose of Aredia in severe hypercalcemia (corrected serum calcium<sup>\*</sup>>13.5 mg/dL) is **90 mg given as a SINGLE DOSE, intravenous infusion over 2 to 24 hours. Longer infusions (i.e., > 2 hours) may reduce the risk for renal toxicity, particularly in patients with pre-existing renal insufficiency. The 90-mg dose must be given by an initial, SINGLE DOSE, intravenous infusion over 24 hours. For select patients 90 mg can be infused over 2 to 24 hours.**

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\*Albumin-corrected serum calcium (CCa,mg/dL) = serum calcium, mg/dL + 0.8 (4.0-serum albumin, g/dL).

#### **Retreatment**

A limited number of patients have received more than one treatment with Aredia for hypercalcemia. Retreatment with Aredia, in patients who show complete or partial response initially, may be carried out 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.** The dose and manner of retreatment is identical to that of the initial therapy.

#### **Paget's Disease**

The recommended dose of Aredia in patients with moderate to severe Paget's disease of bone is 30 mg daily, administered as a 4-hour infusion on 3 consecutive days for a total dose of 90 mg.

#### **Retreatment**

A limited number of patients with Paget's disease have received more than one treatment of Aredia in clinical trials. When clinically indicated, patients should be retreated at the dose of initial therapy.

#### **Osteolytic Bone Lesions of Multiple Myeloma**

The recommended dose of Aredia in patients with osteolytic bone lesions of multiple myeloma is 90 mg administered as a 4-hour infusion given on a monthly basis.

Patients with marked Bence-Jones proteinuria and dehydration should receive adequate hydration prior to Aredia infusion.

Limited information is available on the use of Aredia in multiple myeloma patients with a serum creatinine  $\geq 3.0$  mg/dL.

The optimal duration of therapy is not yet known, however, in a study of patients with myeloma, final analysis after 21 months demonstrated overall benefit (see CLINICAL TRIALS section).

#### **Osteolytic Bone Metastases of Breast Cancer**

The recommended dose of Aredia in patients with osteolytic bone metastases is 90 mg administered over a 2-hour infusion given every 3-4 weeks.

Aredia has been frequently used with doxorubicin, fluorouracil, cyclophosphamide, methotrexate, mitoxantrone, vinblastine, dexamethasone, prednisone, melphalan, vincristine, megestrol, and tamoxifen. It has been given less frequently with etoposide, cisplatin, cytarabine, paclitaxel, and aminoglutethimide. The optimal duration of therapy is not known, however, in two breast cancer studies, final analyses performed after 24 months of therapy demonstrated overall benefit (see CLINICAL TRIALS section).

#### **Preparation of Solution**

##### **Reconstitution**

Aredia is reconstituted by adding 10 mL of Sterile Water for Injection, USP, to each vial, resulting in a solution of 30 mg/10 mL, 60 mg/10 mL, or 90 mg/10 mL. The pH of the reconstituted solution is 6.0 - 7.4. The drug should be completely dissolved before the solution is withdrawn.

##### **Hypercalcemia of Malignancy**

The daily dose must be administered as an intravenous infusion over at least 4 2 to 24 hours for the 60-mg and dose, and 2 to 24 hours for the 90-mg doses. The recommended dose should be diluted in 1000 mL of

sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. This infusion solution is stable for up to 24 hours at room temperature.

***Paget's Disease***

The recommended daily dose of 30 mg should be diluted in 500 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, and administered over a 4-hour period for 3 consecutive days.

***Osteolytic Bone Metastases of Breast Cancer***

The recommended dose of 90 mg should be diluted in 250 mL of sterile 0.45% or 0.9% sodium chloride, USP, or 5% dextrose injection, USP, and administered over a 2-hour period every 3-4 weeks.

***Osteolytic Bone Lesions of Multiple Myeloma***

The recommended dose of 90 mg should be diluted in 500 mL of sterile 0.45% or 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, and administered over a 4-hour period on a monthly basis.

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

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

Aredia reconstituted with Sterile Water for Injection may be stored under refrigeration at 36°-46°F (2°-8°C) for up to 24 hours.

**HOW SUPPLIED**

*Vials* - 30 mg - each contains 30 mg of sterile, lyophilized pamidronate disodium and 470 mg of mannitol, USP.

Carton of 4 vials..... NDC 0083-2601-04

*Vials* - 90 mg - each contains 90 mg of sterile, lyophilized pamidronate disodium and 375 mg of mannitol, USP.

Carton of 1 vial ..... NDC 0083-2609-01

Do not store above 86°F (30°C).

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 **NOVARTIS**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20036/S024**

**MEDICAL REVIEW**

## MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

<b>Application #:</b> NDA 20-036	<b>Application Type:</b> SE2 labeling supplement
<b>Sponsor:</b> Novartis	<b>Proprietary Name:</b> Pamidronate
<b>Investigator:</b> Multiple	<b>USAN Name:</b> Aredia
<b>Category:</b> Bisphosphonate	<b>Route of Administration:</b> Intravenous
<b>Reviewer:</b> Eric Colman	<b>Review Date:</b> 08/13/01

### RELATED APPLICATIONS

Document Date	Application Type	Comments
	NDA 21-223	
	Zoledronate IV 4 mg	
	Treatment of hypercalcemia of malignancy	

### REVIEW SUMMARY:

The question addressed in this supplemental NDA is: Are there data to support the efficacy and safety of 90 mg of pamidronate infused over 2 hours in patients with HCM? The answer comes from three sources: 1) Data on the 17 patients who received pamidronate 90-mg IV over 24 hours (original pamidronate HCM NDA), 2) Data from the zoledronate active-control trials in which pamidronate 90 mg was infused over 2 hours, and 3) Published literature on 60 mg and 90 mg of pamidronate infused over 2-24 hours.

A comparison of the data from the 17 patients treated with pamidronate 90 mg over 24 hours to the 103 patients treated with 90 mg over 2 hours indicates that the safety profiles, in particular renal safety, are similar for these dosing regimens. Efficacy was higher in the 24-hour group than in the 2-hour group, but there were a number of differences between the studies that could have led to a lower relative efficacy in the 2-hour vs. the 24-hour regimens. Two include a higher baseline serum calcium level and a stricter definition of normocalcemia in the 2-hour group vs. the 24-hour group. The 11 literature reports reviewed support the relative efficacy and safety of pamidronate 60-mg and 90-mg when infused over 2-24 hours. Of note, there were no reports of renal toxicity from these studies.

The data submitted in the application along with published literature support the addition of the 2-hour infusion time to the existing dosing instructions for the 90 mg (and the 60 mg) dose of pamidronate. In addition to the Dosage and Administration section of the labeling, language for the Clinical Studies and Adverse Reactions sections have been proposed.

**OUTSTANDING ISSUES:** None

<b>RECOMMENDED REGULATORY ACTION:</b>		<b>N drive location:</b>
<b>New clinical studies</b>	<input type="checkbox"/> <b>Approve</b>	<input type="checkbox"/> <b>Study May Proceed</b>
<b>NDA, Efficacy/Label supplement:</b>	<input checked="" type="checkbox"/> <b>Approve</b>	<input type="checkbox"/> <b>Not Approvable</b>

<b>SIGNATURES:</b> Medical Reviewer: _____	Date: _____
Medical Team Leader: _____	Date: _____

## I. Introduction

During Office-level review of a pending NDA for zoledronate for the treatment of hypercalcemia of malignancy (HCM), it was noted that pamidronate, the active comparator in the zoledronate trials, was infused over 2 hours rather than 24 hours, as recommended in the approved pamidronate labeling<sup>1</sup>. From a regulatory perspective this posed potential problems because Novartis wished to include the pamidronate efficacy and safety data in the zoledronate labeling. This issue was discussed with Novartis during an August 8, 2001, teleconference. At that time it was agreed that an appropriate course of action would be for the company to submit a supplemental NDA requesting the addition of the 2-hour infusion time to the Dosage and Administration section of the pamidronate labeling.

## II. Material Reviewed

My recommendation regarding approvability of this sNDA is based on review of the following:

1. Studies 01 and 03 – the pivotal trials for pamidronate's HCM indication, with particular attention given to the renal safety data from study 01.
2. Study 02 – a supplemental study comparing 60 mg of pamidronate infused over 24 hours to 4 hours.
3. A comparison of the major safety issues, with particular emphasis on renal adverse events, for the pamidronate 90-mg 2-hour infusion groups (from zoledronate studies) with the pamidronate 90 mg 24-hour infusion group (from study 01 from original pamidronate HCM trials).
4. Novartis's Clinical Safety and Epidemiology Database search.
5. Published studies of pamidronate in the treatment of HCM (focused on studies of 15-60 mg of pamidronate infused in less than 24 hours and of 90 mg of pamidronate)

## III. Background – Pivotal Pamidronate Trials for HCM

Pamidronate (referred to as APD during early development) was approved for the treatment of HCM in 1991. Approval was based on data from two clinical studies: 01 and 03, as described below.

**Protocol 01** was a multicenter, randomized, double-blind dose-ranging study of 52 patients with HCM. Patients were randomized to drug if, after 48 hours of IV saline hydration, their corrected serum calcium was  $\geq 12.0$  mg/dl and their serum creatinine was less than 2.6 mg/dl. Fifteen, 20, and 17 patients were randomized to pamidronate 30 mg, 60 mg, and 90 mg, respectively. Baseline corrected serum calcium levels were 13.8 mg/dl, 13.8 mg/dl, and 13.3 mg/dl in the 30 mg, 60 mg, and 90 mg groups, respectively. Study drug was infused IV over 24 hours. By Day 7 following drug infusion, 40%, 61%, and 100% of the patients in the 30-mg, 60-mg, and 90-mg groups, respectively, achieved normal corrected serum calcium levels<sup>2</sup>. Ten to 25% of the patients developed transient fever, hypophosphatemia, hypokalemia, or hypomagnesemia. No patient had an increase in serum creatinine of greater than 25%; in fact, 40% to 77% of patients had decreases in serum creatinine from baseline. Thirteen percent, 16%, and 6% of the 30-mg, 60-mg, and 90-mg subjects, respectively, had increases in creatinine based on pre-defined criteria (see page 4).

**Protocol 03** was a double-blind, double-dummy, active-controlled trial in 65 patients with HCM. Patients were randomized to drug if, after 24 hours of IV saline hydration, their corrected serum calcium was  $\geq 12.0$  mg/dl and their serum creatinine was  $< 2.6$  mg/dl. Thirty patients were randomized to 60 mg of IV pamidronate infused over 24 hours and 35 patients were randomized to etidronate 7.5 mg/kg as a 2-hour IV infusion daily for 3 days. Baseline corrected serum calcium levels were 14.6 mg/dl and 13.8 mg/dl, in the pamidronate and etidronate groups, respectively. By Day 7 following drug treatment, 70% of pamidronate-

<sup>1</sup> During a July, 1997, End-of Phase I meeting between Novartis and the Divisions of Oncology and Metabolic and Endocrine Drug Products, it was agreed that the two pivotal zoledronate HCM active-controlled trials could use an infusion time of less than 24 hours for the pamidronate arms. The possibility of changing the pamidronate labeling with data from these studies was also discussed.

<sup>2</sup> The definition of normocalcemia varied from center to center and ranged from 10.4 mg/dl to 11.0 mg/dl – 10.8 mg/dl was considered normocalcemic in the pivotal zoledronate trials.

treated compared with 41% of etidronate-treated patients achieved normal corrected serum calcium levels (see footnote 2 on previous page). There were no reports of significant elevations in serum creatinine in either treatment group.

**Protocol 02** was submitted as a supplemental NDA in the early 1990s. This study compared the effects of pamidronate 60-mg IV infused over 4 hours and 60 mg IV infused over 24 hours to IV saline treatment. Sixty-nine patients were randomized in equal fashion to one of the three treatment groups. All subjects had received saline hydration for 24 hours prior to drug treatment. Corrected serum calcium levels at baseline were 14.2 mg/dl, 13.7 mg/dl, and 13.7 mg/dl in the pamidronate 4-hour, 24-hour, and saline groups, respectively. By Day 7, 78%, 61%, and 22% of patients in the 60-mg 4-hour infusion, 60-mg 24-hour infusion, and saline infusion, respectively, had normal corrected serum calcium levels. Nine percent of the 4-hour infusion group and 18% of the 24-hour group had increases in serum creatinine using pre-defined criteria (see page 4)

*Comment: The data from Protocol 01 suggest that pamidronate's efficacy is dose-related, with the 90-mg dose providing the greatest benefit. Protocol 02 indicates that reducing the infusion time from 24 to 4 hours does not diminish efficacy (in fact, patients in the 4-hour regimen had a greater response rate than those the 24-hour regimen). In addition, there is no evidence from the three studies that the risk for renal injury is appreciably altered when subjects receive 90 mg vs. 60 mg or 30 mg or when the infusion time is reduced from 24 to 4 hours.*

#### IV. Comparative Safety of the 2-hour and 24-hour 90 mg Pamidronate Regimens

The following section compares relevant safety data for the 90-mg dose of pamidronate when infused over 24 hours (data from study 01, original pamidronate HCM NDA) to 2 hours (data from studies 036 and 037, zoledronate NDA). No statistical comparisons were made.

When interpreting the following data, it should be remembered that there are no head-to-head comparisons of 90-mg pamidronate infused over 2 hours vs. 24 hours. For purposes of this supplement, comparisons between 90 mg 24 hours and 90 mg 2 hours are made across studies. Some key differences between Studies 01 and 036 and 037 that may have affected study results are shown below.

##### 90 mg pamidronate IV over 24 hours (Study 01)

- 17 patients
- 41% of patients Black
- Duration of cancer not recorded
- 48 hours of IV hydration prior to drug
- Baseline serum calcium = 13.3 mg/dl
- PTHrp not measured
- Response defined at Day 7
- Normocalcemia < 11.0 mg/dl
- Excluded if baseline creatinine > 2.6 mg/dl
- 50% received loop diuretics
- Prior exposure to bisphosphonate not recorded

##### 90 mg pamidronate IV over 2 hours (Studies 036 and 037)

- 103 patients
- 17% of patients Black
- 38% with cancer for  $\geq$  12 months
- No pre-drug hydration required
- Baseline serum calcium = 14.0 mg/dl
- 24% with PTHrp > 2 pmol/L
- Response defined at Day 10
- Normocalcemia < 10.8 mg/dl
- Excluded if baseline creatinine > 4.5 mg/dl
- 21% received loop diuretics
- 11% of patients with prior exposure to bisphosphonate

**Comment:** There are a number of differences between studies 01 and 036 and 037 that could account for the lower response rate observed in the 90 mg 2-hour group compared with the 90 mg 24-hour group. Most importantly, the 2-hour group had higher baseline calcium levels and employed a stricter definition of normocalcemia than the 24-hour group.

#### Deaths and Serious Adverse Events

A total of 7/17 (41%) of the 24-hour patients died on-study vs. 20/103 (19%) of the 2-hour subjects. Two of 17 (12%) subjects in the 24-hour group had one or more serious adverse events compared with 43/103 (42%) of the 2-hour subjects.

#### Discontinuations Due to Adverse Events

Eight of 103 (8%) patients in the pamidronate 2-hour group discontinued because of an adverse event and none of the pamidronate 24-hour patients discontinued due to an adverse event.

#### Renal

##### Adverse Events

The following table provides the number and percentage of patients in each group reporting renal adverse events.

NUMBER AND PERCENTAGE OF PATIENTS WITH RENAL ADVERSE EVENTS				
	Zol 4 mg N=86	Zol 8 mg N=98	Pam 90 mg 2 hr N=103	Pam 90 mg 24 hr N=17
N and % of Patients with any Abnormality	13 (15%)	14 (14%)	7 (7%)	7 (41%)
Acute Renal Failure	1 (1.2%)	1 (1%)	0	0
Hyperuricemia	1 (1.2%)	0	2 (1.9%)	0
Anuria	0	1 (1.0%)	0	0
Hematuria	1 (1.2%)	2 (2.0%)	2 (1.9%)	0
Hydronephrosis	1 (1.2%)	0	0	0
Micturition Frequency	1 (1.2%)	0	1 (1.0%)	1 (5.9%)
Obstructive Uropathy	0	0	1 (1.0%)	0
Pyelonephritis	1 (1.2%)	0	0	0
Renal Function Abnormal	4 (4.7%)	3 (3.1%)	1 (1.0%)	0
Uremia	2 (2.3%)	4 (4.1%)	0	0
Urinary Tract Disorder*	1 (1.2%)	0	0	6 (35.3%)
Urinary Retention	3 (3.5%)	2 (2.0%)	1 (1.0%)	0

\*primarily urinary tract infection

#### Serum Creatinine

Approximately 18% of pamidronate 24-hour patients had developed either a serum creatinine of > 4.5 mg/dl or had an increase of at least 0.5 mg/dl from baseline compared with 9.0% of pamidronate 2-hour subjects. Eight percent of the zoledronate 4-mg patients met one of these criteria during the trials.

The following table provides the numbers and percentages of patients who had deterioration in renal function as defined by the following criteria:

Increase in serum creatinine of more than 0.5 mg/dl in patients with baseline levels < 1.4 mg/d  
 Increase in serum creatinine of more than 1.0 mg/dl in patients with baseline levels  $\geq$  1.4 mg/dl  
 A doubling or more of the baseline serum creatinine

NUMBER AND PERCENTAGE OF PATIENTS WITH RENAL FUNCTION DETERIORATION				
	Zol 4 mg N=86	Zol 8 mg N=98	Pam 90 mg 2 hr N=103	Pam 90 mg 24 hr N=17
Number	6	12	10	1
Percentage	7%	13%	10%	6%

**Comment:** The patterns of reporting of renal adverse events were similar for the pamidronate 2-hour and 24-hour dosing regimens. And while 10% of the pamidronate 2-hour subjects had deterioration in renal function (according to pre-defined criteria) compared with 6% of the 24-hour subjects, the small sample size of the 24-hour group makes it difficult to draw firm conclusions. For example, if one additional patient had renal function deterioration in this group the incidence would have doubled (6 to 12%).

#### Minerals and Electrolytes

A larger percentage of patients in the pamidronate 24-hour group compared with the 2-hour group developed hypokalemia (41% vs. 16%), hypocalcemia (12% vs. 2%), hypomagnesemia (29% vs. 5%), hypophosphatemia (47% vs. 2%), and hyperkalemia (6% vs. 4%).

**Comment:** Unlike the pamidronate 2-hour data, the early pamidronate trials did not employ consistent definitions for electrolyte abnormalities, rather it was up to investigator to define a laboratory parameter as "hypo" or "hyper". This was presumably done by referring to local laboratory reference ranges. This may account for the higher incidence of mineral and electrolyte abnormalities noted in the 24-hour group vs. the 2-hour group.

#### V. Novartis's Clinical Safety and Epidemiology Database Search

A search of the Novartis safety database revealed a total of 3,745 adverse event reports for pamidronate including 1,856 spontaneous reports. Eight reports (7 spontaneous and 1 from the literature) met the following criteria:

- Use of pamidronate 90 mg IV for the treatment of HCM.
- Infusion time of 24 hours or less

Only one of these reports was related to renal function – the actual term was deterioration of renal function. Other events included dyspnea, hypocalcemia, drug malabsorption, hypomagnesemia, disease progression, and thrombophlebitis.

#### VI. Published Literature

The following two tables summarize the published literature on low-to-moderate (15-60mg) and high (90mg) doses of pamidronate.

SUMMARY OF PUBLISHED STUDIES OF 15 TO 60 MG OF PAMIDRONATE (INFUSED IN LESS THAN 24 HR) IN THE TREATMENT OF HYPERCALCEMIA OF MALIGNANCY						
Title and Year of Publication	Dosing Regimen	N	Pre-Dose Hydration	Efficacy*	Cr ↑#	Comments
APD for hypercalcemia of breast cancer - 1987	15 mg - 2 hr	22	3 L saline x 48 hr	78%	0%	Fever in 2 patients
Infusion rate and PK of IV pamidronate in the treatment of tumor-induced hypercalcemia - 1987	60 mg - 2 vs. - 4 hr 60 mg - 8 vs. - 24 hr	50	Yes - details not provided	> 90% > 90%	0%	Fever in 4 patients

Dose/response of APD in tumor-associated hypercalcemia - 1987	0.01 mg/kg/day - 2 hr 0.05 mg/kg/day - 2 hr 0.25 mg/kg/day - 2 hr 0.75 mg/kg/day - 2 hr 1.5 mg/kg/day - 2 hr 3.0 mg/kg/day - 2 hr	18	Saline x 48 hr	33% 67% 100% 100% 100% 67%	0%	↓ Platelets in one patient  Fever and ↓ BP in one 3.0-mg dose patient
Single high-dose infusions of APD for severe malignant hypercalcemia - 1989	45 mg - 3 hr	20	2 L saline	75%	0%	Dyspnea in one patient
Single dose vs. daily IV APD for hypercalcemia of malignancy - 1988	60 mg - 8 hr 30 mg - 4 hr 15 mg - 2 hr	30	Yes - details not provided	> 90% in all groups	0%	Fever in 5 patients
Fast (4-h) or slow (24-h) infusions of APD as single shot treatment of hypercalcemia - 1990	1 mg/kg - 4 hr 1 mg/kg - 24 hr max dose = 75 mg	25	unclear	Retreat req in 2/2 hr gp 5/24 hr gp	0%	8 patients with impaired renal fct at baseline - no renal AEs

\* achieving a normal calcium level # elevation in serum creatinine (usually defined as an increase of > 0.5 mg/dl)

SUMMARY OF PUBLISHED STUDIES OF 90 MG OF PAMIDRONATE IN THE TREATMENT OF HYPERCALCEMIA OF MALIGNANCY						
Title	Dosing Regimen	N	Pre-Dose Hydration	Efficacy*	Cr ↑#	Comments
Dose response in the treatment of hypercalcemia of malignancy by a single infusion of ADP - 1988	30 mg - 24 hr 45 mg - 24 hr 60 mg - 24 hr 90 mg - 24 hr	52	2 L saline x 24 hr	67% NR NR 92%	0%	Asymptomatic hypocalcemia in 6/26 patients in 90 mg group
A comparison of low vs. high dose pamidronate in cancer-associated hypercalcemia - 1991	30 mg - 4 hr 90 mg - 24 hr	32		63% 50%	NR	
Pamidronate vs. mithramycin in the management of tumor-associated hypercalcemia - 1992	30-90 mg - 12 hr 1.25 mg mithramycin	25		100% 25%	0%	
Single-dose IV therapy with pamidronate for the treatment of hypercalcemia of malignancy - 1993	30 mg - 24 hr 60 mg - 24 hr 90 mg - 24 hr	50	Saline x 48 hr	40% 61% 100%	0%	↓ phosphate in 22 patients
A randomized double-blind comparison of IV pamidronate and clodronate in the hypercalcemia of malignancy - 1995	90 mg - 4 hr 1500 mg clodronate	20	Saline x 48 hr	100% 80%	0%	↓ lymphocyte count

\* achieving a normal calcium level # elevation in serum creatinine (usually defined as an increase of > 0.5 mg/dl)

**Comment:** The data in the above tables suggest that single doses of 60 and 90 mg of pamidronate infused over 2 to 24 hours are relatively efficacious and safe regimens to treat hypercalcemia of malignancy.

There are no head-to-head comparisons of pamidronate infused over 2 hours vs. 24 hours. There is, however, a published study of IV alendronate comparing the effects of 10 mg infused over 2 hours to 24 hours in 20 patients with HCM<sup>3</sup>.

Briefly, 20 patients with HCM were randomized in equal fashion to receive 10 mg of IV alendronate over 2 hours or 24 hours. Patients were eligible for treatment if their corrected serum calcium after 36 hours of IV hydration was at least 12.0 mg/dl. Complete or partial responses were observed in 70% of the 2-hour group and 90% of the 24-hour group (the day at which response was assessed is not clearly defined in the paper). The authors state that there was, "no evidence of renal toxicity and renal function usually improved.....Only one patient showed persistent worsening of renal function during the study, followed by acute renal failure on day 21, just before death. This was probably due to neoplastic infiltration of the

<sup>3</sup> Zysset E, et al. Comparison of a rapid (2-h) versus a slow (24-h) infusion of alendronate in the treatment of hypercalcemia of malignancy. Bone and Mineral 1992; 18: 237-249.

kidney and was considered as probably not drug related." There is no mention of which treatment this patient received.

## **VII. Discussion**

During a July 1997, meeting between The Divisions of Oncology and Metabolic and Endocrine Drugs with Novartis, it was agreed that the pivotal, active-controlled zoledronate trials could employ an infusion time of less than 24 hours for the pamidronate arms. The company chose a 2-hour infusion because this reflected standard clinical practice, even though the 90-mg dose is only approved as a 24-hour infusion.

During Office-level review of the pending zoledronate HCM NDA, it was noted that the pivotal trials compared the efficacy and safety of IV zoledronate infused over 5 minutes to IV pamidronate infused over 2 hours. This issue was discussed with Dr. John Jenkins, Director of ODEII, and subsequently with Novartis. An agreement was reached that the company would submit a supplemental NDA for pamidronate that contained justification to alter (i.e., add 2 hours as an option) the Dosing and Administration section of the labeling.

The 90-mg dose of pamidronate is currently approved for the treatment of moderate and severe HCM. The label states that this dose must be infused over 24 hours. This recommendation, based on data from 17 patients, reflected concern regarding the potential for renal toxicity, which had been reported following rapid IV administration of bisphosphonates in patients with HCM. Since the time of pamidronate's approval, many studies have examined the efficacy and safety of pamidronate when infused from 2 to 24 hours.

The data reviewed in this labeling supplement support the efficacy and safety of single 90-mg pamidronate infusions given from 2 to 24 hours. While there are no head-to-head comparisons of the safety and efficacy of pamidronate 90 mg infused over 2 vs. 24 hours, a comparison of the 90-mg 24-hour data (original pamidronate HCM NDA) with the pamidronate 2-hour data (zoledronate HCM NDA) provides reassurance that, compared with the 24-hour regimen, the 2-hour infusion does not increase the risk for renal toxicity, or other significant adverse events. The lower efficacy in the pamidronate 2-hour group (70% complete response rate) than in the 24-hour group (100%) may be due to a number of factors including a higher baseline corrected serum calcium level in the 2-hour group (14.0 mg/dl vs. 13.3 mg/dl), less frequent use of loop diuretics in the 2-hour group (21% vs. 50%), and the use of a stricter definition of normocalcemia in the 2-hour group (< 10.8 mg/dl vs. < 11.0 mg/dl). It should also be kept in mind that the estimate of pamidronate's efficacy when infused over 24 hours was based on only 17 patients.

### **Conclusion and Recommendation**

I believe the data reviewed above support approval of a 2-24 hour dosing regimen for the 90-mg (and the 60 mg) dose of pamidronate for the treatment of hypercalcemia of malignancy. I recommend that this supplemental NDA be approved.

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Eric Colman, MD

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20036/S024**

**ADMINISTRATIVE DOCUMENTS**

**Division of Metabolic and Endocrine Drug Products**

**CONSUMER SAFETY OFFICER REVIEW**

**Application Number:** 20-036/S-024

**Name of Drug:** Aredia (pamidronate disodium for injection)

**Sponsor:** Novartis Pharmaceuticals Corporation

**Material Reviewed**

**Submission Date(s):** August 16, 2001, containing revised draft labeling

**Receipt Date(s):** Fax was received on August 16, 2001

**Background and Summary Description:**

The labeling for S-024 was compared to the currently approved labeling (Identifier 665338 Revision Date 9/98) approved with S-016 on September 22, 1998; A & R April 3, 2000.

**Review**

All appropriate changes were made to the revised draft labeling to change the administration rate for the infusion of Aredia from 24 hours to 2 to 24 hours. This change applies to the indications for the treatment of moderate and severe hypercalcemia of malignancy, with or without bone metastases.

The labeling review did reveal one error in the revised draft label. In the *Reconstitution* section, the first sentence reads, "Aredia is reconstituted by adding 10 mL of Sterile Water for Injection, USP, to each vial, resulting in a solution of 30 mg/10 mL, 60 mg/10 mL, or 90 mg/10mL. A 60 mg vial is not approved, and the FPL submitted on August 16, 2001, does not include the 60 mg/10mL reconstitution result.

**Conclusions**

The AP letter will include a request to remove the 60 mg/10 mL result of reconstitution from the label, when FPL is submitted.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

EXCLUSIVITY SUMMARY for NDA # 20-036 SUPPL # 024  
Trade Name Aredia Injection Generic Name pamidronate  
disodium for injection  
Applicant Name Novartis Pharmaceutical Inc. HFD- 510  
Approval Date August 20, 2001

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/\_\_\_/ NO /X/

b) Is it an effectiveness supplement? YES /x/ NO /\_\_\_/

If yes, what type(SE1, SE2, etc.)? SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X/ NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

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If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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e) Has pediatric exclusivity been granted for this Active Moiety?

YES /  / NO /  /

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**



If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / \_\_\_ /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain: \_\_\_\_\_

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /X/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 036

Investigation #2, Study # 037

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /X/ NO /\_\_\_/

Investigation #2 YES /X/ NO /\_\_\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA #	<u>21-223</u>	Study #	<u>036</u>
NDA #	<u>21-223</u>	Study #	<u>037</u>
NDA #	_____	Study #	_____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / <u>  </u> /	NO / <u>X</u> /
Investigation #2	YES / <u>  </u> /	NO / <u>X</u> /
Investigation #3	YES / <u>  </u> /	NO / <u>  </u> /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA #	_____	Study #	_____
NDA #	_____	Study #	_____
NDA #	_____	Study #	_____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #	<u>  </u>	Study #	_____
Investigation #	<u>  </u>	Study #	_____
Investigation #	<u>  </u>	Study #	_____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND #  YES / X / NO / \_\_\_ / Explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Investigation #2  
IND #  YES / X / NO / \_\_\_ / Explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES / \_\_\_ / Explain \_\_\_\_\_ NO / \_\_\_ / Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Investigation #2  
YES / \_\_\_ / Explain \_\_\_\_\_ NO / \_\_\_ / Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/                      NO / X /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Title: \_\_\_\_\_

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Office or Division Director

\_\_\_\_\_  
Date

cc:  
Archival NDA  
HFD- /Division File  
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