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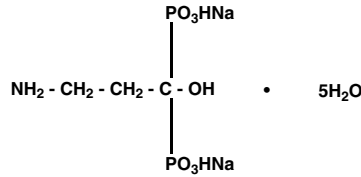
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**Aredia®**pamidronate disodium for injection  
For Intravenous Infusion

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>5</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 ± SD of 46 ± 16% of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean ± SD elimination half-life is 28 ± 7 hours. Mean ± SD total and renal clearances of pamidronate were 107 ± 50 mL/min and 49 ± 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.

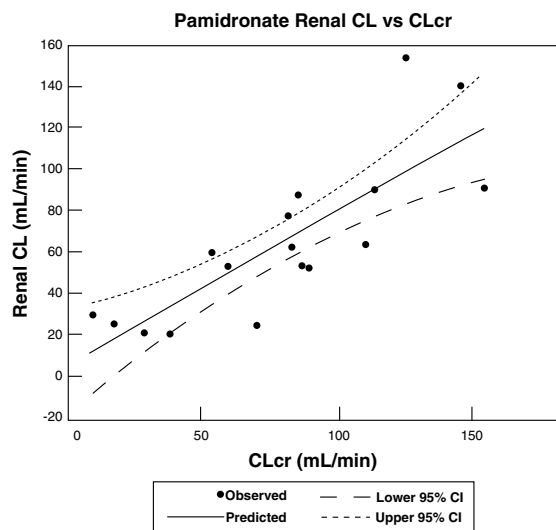
**Pediatric**

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.

Dose (infusion rate)	Maximum Concentration (µg/mL)	Percent of dose excreted in urine	Total Clearance (mL/min)	Renal Clearance (mL/min)
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 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 ≥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 (≥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 ≥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 etidronate disodium as a 2-hour intravenous infusion daily for 3 days. Thirty patients were randomized to receive Aredia and 35 to receive etidronate disodium.

The mean baseline-corrected serum calcium for the Aredia 60-mg and etidronate disodium 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 etidronate disodium group had normal-corrected serum calcium levels (P<0.05). When partial responders (≥15% decrease of serum calcium from baseline) were also included, the response rates were 97% for the Aredia group and 65% for the etidronate disodium group (P<0.01). Mean-corrected serum calcium for the Aredia and etidronate disodium 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 etidronate disodium group still had normal-corrected serum calcium levels, or maintenance of a partial response. For responders in the Aredia and etidronate disodium 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.

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)
Baseline	
24	-0.3
48	-1.5
72	-2.6
96	-3.5
168	-4.1

<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 ≥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).

**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 hydroxyproline/creatinine ratios (UOHP/C) are summarized in the following table:

% Decrease	Percent of Patients With Significant % Decreases in SAP and UOHP/C					
	SAP			UOHP/C		
≥50	15 mg	45 mg	90 mg	15 mg	45 mg	90 mg
≥30	26	33	60	15	47	72
	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 antineoplastic 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<0.02). The times to the first SRE occurrence, pathologic fracture, and radiation to bone were significantly longer in the Aredia group (P=0.01, 0.06, and 0.46, respectively). Moreover, fewer Aredia patients suffered any pathologic fracture (17% vs 30%, P=0.04) or needed radiation to bone (14% vs 22%, P=0.49).

In addition, decreases in pain scores from baseline occurred at the last measurement for those Aredia patients with pain at baseline (P=0.026) 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=0.01) and ECOG performance status (P=0.011) 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=0.015). In addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for Aredia patients vs placebo patients (P=0.008), and time to first SRE was significantly longer in the Aredia group compared to placebo (P=0.016). Fewer Aredia patients suffered vertebral pathologic fractures (16% vs 27%, P=0.005). 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 they 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
	185	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 <sup>†</sup>		.018 <sup>†</sup>		.021		.013 <sup>†</sup>		.040 <sup>†</sup>	
Proportion of patients having an SRE	46%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001 <sup>†</sup>		.014 <sup>†</sup>		.094		.058 <sup>†</sup>		.054 <sup>†</sup>	
Median Time to SRE (months)	13.9	7.0	NR**	14.2	25.8	13.3	10.9	7.4	NR**	23.4	20.6	12.8
P-Value	<.001		<.001 <sup>†</sup>		.009 <sup>†</sup>		.118		.016 <sup>†</sup>		.113 <sup>†</sup>	

<sup>†</sup>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 following table:

	Mean Change (Δ) 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 Δ	N	Mean Δ	N	Mean Δ	
Pain Score	175	+0.93	183	+1.69	.050	173	+0.50
Analgesic Score	175	+0.74	183	+1.55	.009	173	+0.90
ECOG PS	178	+0.81	186	+1.19	.002	175	+0.95
Spitzer QOL	177	-1.76	185	-2.21	.103	173	-1.86

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 ≥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 ≥50% in at least 50% of patients, and by ≥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).

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<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

**Paget's Disease**  
Transient mild elevation of temperature >1 °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:** Arthritis, 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		Aredia® 90 mg over 2 hours		All Aredia® 90 mg	
	N=205 %	Placebo N=187 %	N=367 %	Placebo N=386 %	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>Musculoskeletal 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 Respiratory 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.

**Renal Toxicity**  
In a study of the safety and efficacy of Aredia 90 mg (2 hour infusion) versus Zometa 4 mg (15 minute infusion) in bone metastases patients with multiple myeloma or breast cancer, renal deterioration was defined as an increase in serum creatinine of 0.5 mg/dL for patients with normal baseline creatinine (<1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (≥1.4 mg/dL). The following are data on the incidence of renal deterioration in patients in this trial. See Table below.

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Patient Population/Baseline Creatinine	Aredia® 90 mg/2 hours		Zometa® 4 mg/15 minutes	
	n/N	(%)	n/N	(%)
Normal	20/246	(8.1%)	23/246	(9.3%)
Abnormal	2/22	(9.1%)	1/26	(3.8%)
Total	22/268	(8.2%)	24/272	(8.8%)

\*Patients were randomized following the 15-minute infusion amendment for the Zometa arm.

### 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). Cases of osteonecrosis (primarily of the jaws) have been reported since market introduction. Osteonecrosis of the jaws has other well documented multiple risk factors. It is not possible to determine if these events are related to Aredia or other bisphosphonates, to concomitant drugs or other therapies (e.g., chemotherapy, radiotherapy, corticosteroid), to patient's underlying disease, or to other comorbid risk factors (e.g., anemia, infection, preexisting oral disease).

### 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 hypercalcemia that required intravenous and/or oral administration of calcium. **Single doses of Aredia should not exceed 90 mg and the duration of the intravenous infusion should be no less than 2 hours. (See WARNINGS.)**

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

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