CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-036/S030

Trade Name: Aredia

Generic Name: (pamidronate disodium for injection)

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: February 2, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-036/S030

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-036/S030

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-036/S-030

Novartis Pharmaceuticals Corporation
Attention: Annmarie Petraglia
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Petraglia:

Please refer to your supplemental new drug application dated November 15, 2004, received November 16, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aredia (pamidronate disodium for injection).

This "Changes Being Effected" supplemental new drug application provides for a new subsection entitled **Osteonecrosis of the Jaw** in the **PRECAUTIONS** section of the package insert.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 15, 2004.

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

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
2/2/05 09:50:21 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-036/S030

LABELING

FPO

FPO

NOVARTIS

T2004-70

Aredia®

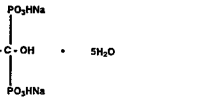
pamidronate disodium for injection
For Intravenous Infusion

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 $C_3H_9NO_7P_2Na_2{\cdot}5H_2O$ 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.

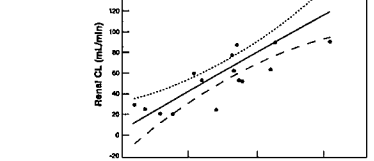
Pediatric

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

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7). Each patient received a single 90-mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC (53%) and C_{max} (29%), and decreased plasma clearance (33%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 to 36 hours after drug infusion. Because Aredia is administered on a monthly basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function. Aredia has not been studied in patients with severe hepatic impairment.

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)

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 (0.67, 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, decreased 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 ≥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.

Change in Corrected Serum Calcium by Time from Initiation of Treatment

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)		
	Aredia®	Etidronate Disodium	P-Value†
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

†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:

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

	SAP			UOHP/C		
% Decrease	15 mg	45 mg	90 mg	15 mg	45 mg	90 mg
≥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%, $P=.040$).

In addition, decreases in pain scores became 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 or 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:

	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
N	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	1.8	2.2
P-Value	<.001		<.001†		.018†		.021		.013†		.040†	
Proportion of patients having an SRE	48%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001†		.014†		.094		.058†		.054†	
Median Time to SRE (months)	13.9	7.0	NR**	14.2	25.8	13.3	10.9	7.4	NR**	23.4	20.6	12.8
P-Value	<.001		<.001†		.009†		.118		.018†		.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 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	P-Value*	N	Mean Δ	N	Mean Δ	P-Value*
Pain Score	175	+0.93	183	+1.69	.050	173	+0.50	179	+1.60	.007
Analgesic Score	175	+0.74	183	+1.55	.009	173	+0.90	179	+2.28	<.001
ECOG PS	178	+0.81	186	+1.19	.002	175	+0.95	182	+0.90	.773
Spitzer QOL	177	-1.76	185	-2.21	.103	173	-1.86	181	-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 ≥2 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 statistical 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

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF AREDIA SHOULD NOT EXCEED 90 MG (see DOSAGE AND ADMINISTRATION for appropriate infusion durations).

Bisphosphonates, including Aredia, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure.

Patients who receive Aredia should have serum creatinine assessed prior to each treatment. Patients treated with Aredia for bone metastases should have the dose withheld if renal function has deteriorated. (See DOSAGE AND ADMINISTRATION.)

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 ≥10 mg/kg. In the second study, slight renal tubular necrosis was observed 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 ≥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, over a 1-hour infusion, once a week, for 3 months followed by a 1-month recovery period. In rats, nephrotoxicity was observed at ≥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 ≥6 mg/kg and renal tubular degeneration at ≥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).

PREGNANCY: AREDIA SHOULD NOT BE USED DURING PREGNANCY

Aredia may cause fetal harm when administered to a pregnant woman. (See PRECAUTIONS, Pregnancy Category D.)

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

Studies conducted in young rats have reported the disruption of dental denitine 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.

Renal Insufficiency

Aredia is excreted intact primarily via the kidney, and the risk of renal adverse reactions may be greater in patients with impaired renal function. Patients who receive Aredia should have serum creatinine assessed prior to each treatment. In patients receiving Aredia for bone metastases, who show evidence of deterioration in renal function, Aredia treatment should be withheld until renal function returns to baseline (see WARNINGS and DOSAGE AND ADMINISTRATION).

Aredia has not been tested in patients who have class Dc renal impairment (creatinine >5.0 mg/dL), and has been tested in few multiple myeloma patients with serum creatinine ≥3.0 mg/dL. (See also CLINICAL PHARMACOLOGY, Pharmacokinetics.) For the treatment of bone metastases, the use of Aredia in patients with severe renal impairment is not recommended. In other indications, clinical judgment should determine whether the potential benefit outweighs the potential risk in such patients.

Osteonecrosis of the Jaw

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

A dental examination with appropriate preventive dentistry should be considered prior to

treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).

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

Laboratory Tests
Patients who receive Aredia should have serum creatinine assessed prior to each treatment. Serum calcium, electrolytes, phosphate, magnesium, 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.

Caution is indicated when Aredia is used with other potentially nephrotoxic drugs.

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 D (See WARNINGS)
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 non-teratogenic embryo/fetal effects in rats and rabbits, it should not be given to women during pregnancy.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

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 in patients treated with 90 mg of Aredia. 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.

Five of 231 patients (2%) who received Aredia during the 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 investigator. 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.

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 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 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				
	Aredia®			Etidronate Disodium	Saline
	60 mg over 24 hr n=23	60 mg over 24 hr n=73	90 mg over 24 hr n=17	7.5 mg/kg x 3 days n=35	n=23
General					
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
Gastrointestinal					
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
Gastrointestinal hemorrhage	0	0	6	0	0
Nausea	4	0	18	6	0
Stomatitis	0	1	0	3	0
Vomiting	4	0	0	0	0
Respiratory					
Dyspnea	0	0	0	3	0
Rales	0	0	6	0	0
Rhinitis	0	0	6	0	0
Upper respiratory infection	0	3	0	0	0
CNS					
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
Cardiovascular					
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
Endocrine					
Hypothyroidism	0	0	6	0	0
Hemic and Lymphatic					
Anemia	0	0	6	0	0
Leukopenia	4	0	0	0	0
Neutropenia	0	1	0	0	0
Thrombocytopenia	0	1	0	0	0
Musculoskeletal					
Myalgia	0	1	0	0	0
Urogenital					
Uremia	4	0	0	0	0
Laboratory Abnormalities					
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: 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 %
General						
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
Digestive System						
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	18.6	19.8	46.3	39.1	35.7	32.8
Hemic and Lymphatic						
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
Musculoskeletal System						
Arthralgias	10.7	7.0	15.3	12.7	13.6	10.6
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
CNS						
Anxiety	7.8	9.1	18.0	16.8	14.3	14.3
Headache	24.4	19.8	27.2	23.8	26.2	22.3
Insomnia	17.1	17.2	25.1	19.4	22.2	19.0
Respiratory System						
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
Urogenital System						
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.

Incidence of Renal Function Deterioration in Multiple Myeloma and Breast Cancer Patients with Normal and Abnormal Serum Creatinine at Baseline*

Patient Population/Baseline Creatinine	Aredia® 90 mg/2 hours n/N	(%)	Zometa® 4 mg/15 minutes 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). (See PRECAUTIONS.)

OVERDOSAGE

There have been several cases of drug misadministration 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. **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

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 preexisting renal insufficiency.

Severe Hypercalcemia
The recommended dose of Aredia in severe hypercalcemia (corrected serum calcium*>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 preexisting renal insufficiency.

*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 ≥3.0 mg/dL.

Patients who receive Aredia should have serum creatinine assessed prior to each treatment. Treatment should be withheld for renal deterioration. In a clinical study, renal deterioration was defined as follows:

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

In this clinical study, Aredia treatment was resumed only when the creatinine returned to within 10% of the baseline value.

The optimal duration of therapy is not yet known, however, in a study of patients with myeloma, final analysis after 21 months demonstrated overall benefits (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.

Patients who receive Aredia should have serum creatinine assessed prior to each treatment. Treatment should be withheld for renal deterioration. In a clinical study, renal deterioration was defined as follows:

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

In this clinical study, Aredia treatment was resumed only when the creatinine returned to within 10% of the baseline value.

The optimal duration of therapy is not known, however, in two breast cancer studies, final analyses performed after 24 months of therapy demonstrated overall benefits (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 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.

Method of Administration
DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF AREDIA SHOULD NOT EXCEED 90 MG. (SEE WARNINGS.)

There must be strict adherence to the intravenous administration recommendations for Aredia in order to decrease the risk of deterioration in renal function.

Hypercalcemia of Malignancy
The daily dose must be administered as an intravenous infusion over at least 2 to 24 hours for the 60-mg and 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 2°C-8°C (36°F-46°F) 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 30°C (86°F).

T2004-70
REV: AUGUST 2004 Printed in U.S.A. 5000083
5000084

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-036/S030

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: 20-036/S-030

Name of Drug: Aredia (pamidronate disodium injection)

Sponsor: Novartis Pharmaceuticals Corporation

Material Reviewed

Submission Dates:

- November 15, 2004, containing final printed labeling (FPL) of the package insert.

Background and Summary Description:

This CBE-0 supplemental application was submitted to the Division by Novartis in response to a number of spontaneous reports of osteonecrosis of the jaw associated with use of I.V. bisphosphonates. The firm proposes to add a new subsection "**Osteonecrosis of the Jaw**" to the **Precautions** section of the package insert.

Review

The submitted FPL (Identifier T2004-70 5000084, Revised August, 2004) was compared to the FPL submitted September 26, 2003 (Identifier T2003-68 89002606, Revised September, 2003). The labels are identical, except for the following:

A new subsection, **Osteonecrosis of the Jaw** is added to the **PRECAUTIONS** section of the package insert. The new subsection reads:

> "Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.
>
> A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).

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

Additional information in the *Hepatic Insufficiency* subsection of the **Clinical Pharmacology** section was approved on October 9, 2003 (Supplement 020), and is not in the FPL submitted on September 26, 2003 for supplement 029. This language is included in supplement 30, and is acceptable. This paragraph reads:

> "The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7). Each patient received a single 90 mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC (53%) and Cmax (29%), and decreased plasma clearance (33%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 to 36 hours after drug infusion. Because Aredia is administered on a monthly basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function. Aredia has not been studied in patients with severe hepatic impairment."

Conclusions

Issue an approval letter.

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Randy Hedin
2/1/05 02:17:41 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-036/S-030

CBE-0 SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attn: Annmarie Petraglia
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Petraglia:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Aredia® (pamidronate disodium injection)
NDA Number:	20-036
Supplement number:	S-030
Date of supplement:	November 15, 2004
Date of receipt:	November 16, 2004

This supplemental application, submitted as "Supplement - Changes Being Effected," proposes final printed labeling including the FDA requested statement on osteonecrosis of the jaw in the PRECAUTIONS section of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 15, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 16, 2005.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Randy Hedin
12/10/04 01:27:03 PM