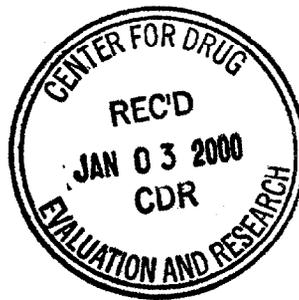


BY FEDERAL EXPRESS

December 29, 1999



Mitchall G. Clark
4365 McConnell Avenue
Los Angeles, CA 90066
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Fax. (310) 398 1714

Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Citizen Petition
Pamidronate Disodium Injection

Dear Sir

Attached are four (4) copies of a Citizen Petition requesting that a change in dosage form of Pamidronate Disodium Injection be considered suitable for submission as an Abbreviated New drug Application (ANDA).

If you have any questions please call the undersigned on 310 391 7908.

Yours sincerely,

A handwritten signature in black ink that reads "m. Clark".

Mitchall G. Clark

00P-0091

CP1

CITIZEN PETITION

The undersigned submits this petition under section 505(j)(2)(C) of the Federal Food Drug, and Cosmetic Act and 21 CFR 314.93, and 10.30 to request the Commissioner of Food and Drugs to grant the Petitioner permission to file an Abbreviated New Drug Application (ANDA) for the Petitioner's Pamidronate Disodium Injection 3 mg/mL, and 9 mg/mL in a ready to use solution for injection.

A. ACTION REQUESTED

This petition seeks a determination that the proposed Pamidronate Disodium Injection 3 mg/mL and 9 mg/mL, in a ready to use solution for injection is suitable for evaluation under an ANDA. This preservative free product is presented in 10 mL vials containing the equivalent to 30 mg and 90 mg of Pamidronate Disodium respectively. This Petition further requests a waiver from the need to conduct clinical studies in pediatric patients, as described in the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule published, December 2, 1998, in the Federal Register (Pediatric Rule)(63 FR 66632).

B. STATEMENT OF GROUNDS

The reference product, Aredia® (Pamidronate Disodium for Injection, 30 mg and 90 mg per vial) by Novartis Pharmaceuticals Corporation is a lyophilized product that requires reconstitution prior to use. The proposed product, Pamidronate Disodium Injection 3 mg/mL and 9 mg/mL in 10 mL vials is a ready to use solution.

The proposed product is equivalent in use, dosage, and route of administration to the listed drug Aredia, and the concentration of the solution product is in accordance with the FDA approved labeling for Aredia (attachment 1).

The formulations of Aredia and the proposed Pamidronate Disodium Injection are presented in Table 1.

Table 1
Comparison of the Reference and the Proposed Product

Ingredient	30 mg per Vial		90 mg per Vial	
	Aredia	Proposed Product	Aredia	Proposed Product
Pamidronate Disodium	30 mg	-	90 mg	-
Pamidronic Acid	-	25.27 mg ¹	-	75.80 mg ¹
Sodium Hydroxide	-	8.60 mg	-	25.80 mg
Phosphoric Acid ²	qs	qs	qs	qs
Mannitol	470 mg	470 mg	375 mg	375 mg
Water for Injection	-	10 mL	-	10 mL

¹Equivalent to Pamidronate Disodium 30 mg and 90 mg respectively

²Phosphoric Acid used for pH adjustment

Citizen Petition
Pamidronate Disodium Injection

As can be seen from Table 2, the amount of the pamidronate species is identical in the Aredia® (Pamidronate Disodium for Injection) and the proposed Pamidronate Disodium Injection. The pH of the proposed solution is identical and is in the normal pH range for therapeutic products.

There are no differences between the reconstituted Aredia and the proposed product as shown in Table 2.

Table 2: Comparison of Reconstituted Aredia and the Proposed Product.

Ingredient	30 mg per Vial		90 mg per Vial	
	Aredia	Proposed Product	Aredia	Proposed Product
Pamidronic Acid	25.27 mg	25.27 mg	75.80 mg	75.80 mg
Sodium ions	4.9 mg	4.9 mg	14.8 mg	14.8 mg
Phosphoric Acid ¹	qs	qs	qs	qs
Mannitol	470 mg	470 mg	375 mg	375 mg
Water for Injection*	10 mL	10 mL	10 mL	10 mL
pH	6.5	6.5	6.5	6.5

*Powder is reconstituted with 10 mL Water for Injection

The proposed product will also eliminate the necessity for reconstitution and mixing prior to use. This will avoid the possibility of improper reconstitution and mixing of the powder and minimize aseptic manipulations of the product, thereby reducing the chance of contamination.

The petitioner also requests a waiver from the need to conduct clinical studies in pediatric patients in support of this petition to change dosage form. Under the regulations cited in Part A of this petition, waivers are granted if: (1) The product (a) did not represent a meaningful therapeutic benefit over existing treatments, and (b) was not likely to be used in a substantial number of pediatric patients as a whole, or was not likely to be used in a substantial number of one or more pediatric subpopulations.

The petitioner submits that the requested change in dosage form described above satisfies the requirements for a waiver from the need for clinical studies in the pediatric population for the following reasons:

- a) The change in dosage form from pamidronate disodium lyophilized powder to a ready to use aqueous form of pamidronate disodium is a pharmaceutical change only. The proposed product is identical to the reference product (Aredia) when Aredia is reconstituted as described in the labeling. The change does not represent a meaningful therapeutic benefit over the reference product or other existing treatments.
- b) Pamidronate disodium is indicated for use in patients with Paget's Disease; in hypercalcemia of malignancy; and in osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma. All of these diseases are primarily diseases of the adult population, therefore pamidronate disodium will not be used in a substantial number (>50,000) of pediatric patients. Evidence to support this statement has been obtained from The Center for Disease Control and Statistics, Vital and Health Statistics, Series 13, No. 138 (published September 1998) (Attachment 2); from Harrison's Principles of Internal Medicine, 14th Edition, Page 713 (Attachment 3); and from the NCI SEER Pediatric Monograph (Attachment 4).

Citizen Petition
Pamidronate Disodium Injection

Provided in attachment 2 is a listing of estimates of the number of hospital discharges from short-stay hospitals, by ICD-9-CM code, sex and age of patient. The ICD-9-CM code for Paget's Disease is 731.0, and for hypercalcemia is 275.4.

There were approximately 18,000 hospital discharges for patients age between 15 and 44 years diagnosed with 'hypercalcemia'. No statistics were identified for the specific diagnosis of hypercalcemia of malignancy. For patients under 15 years, no numbers are provided because the estimate of diagnosis is less than 5000. Therefore, based on these estimates, the population of pediatric patients with hypercalcemia of malignancy is expected to be considerably less than 23,000 (18,000 + 5,000 patients), and is most probably less than 5000 patients. The data also support the fact that hypercalcemia of malignancy is a disease of aging, and therefore would occur at a low frequency in the pediatric population, especially where the disease is associated with malignancy.

Paget's Disease has the ICD-9-CM code 731.0. No occurrences of this disease were recorded in the samples used to estimate the number of diagnoses of this disease in patients below the age of 44 years. Paget's disease, like hypercalcemia of malignancy is a disease of aging, therefore it is reasonable to assume, with support from the CDC statistics, that this disease is very rare in the pediatric population, and certainly occurs in less than 50,000 pediatric patients.

Harrison's (Attachment 3) states that multiple myeloma increases with age and is rare below age 40. An incidence of 4 in 100,000 is quoted for this age group. Further, malignancies of the bone are reported in only 650-700 children and adolescents younger than 20 years in the United States (Attachment 4).

For all of the reasons presented in this statement of grounds, it is believed that the proposed Pamidronate Disodium Injection 3 mg/mL and 9 mg/mL in 10 mL vials is suitable for evaluation under an ANDA.

C ENVIRONMENTAL IMPACT

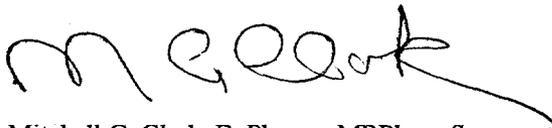
Action on an ANDA is categorically excluded from the requirements of an environmental assessment or impact statement under 21 CFR 25.31 (a).

D ECONOMIC IMPACT

Not Applicable

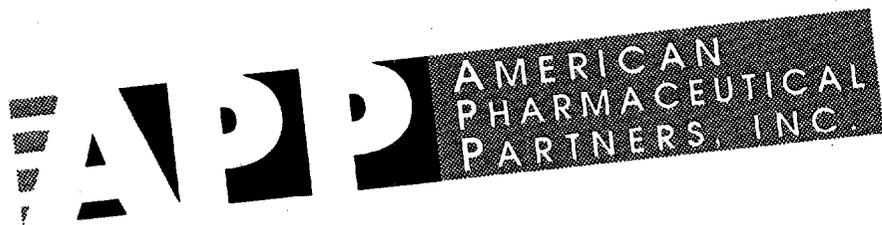
E CERTIFICATION

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all the information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.



Mitchell G. Clark, B. Pharm., MRPharmS.
4365 McConnell Avenue,
Los Angeles, CA 90066

Tel (310) 391 7908



INNOVATOR'S LABELING

Aredia®

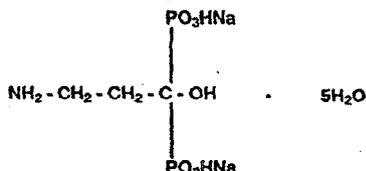
pamidronate disodium for injection
For intravenous infusion

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 $\text{C}_3\text{H}_5\text{NO}_7\text{P}_2\text{Na}_2 \cdot 5\text{H}_2\text{O}$ 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 \pm SD body retention of pamidronate was calculated to be $54 \pm 16\%$ of the dose over 120 hours.

Metabolism

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

Excretion

After administration of 30, 60, and 90 mg of Aredia over 4 hours, and 90 mg of Aredia over 24 hours, an overall mean \pm SD of $46 \pm 16\%$ of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean \pm SD elimination half-life is 28 ± 7 hours. Mean \pm 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.

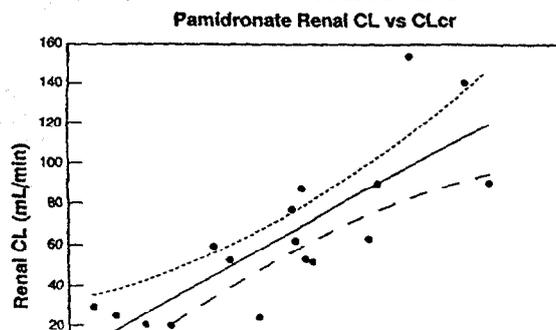
Pediatric

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.



After intravenous administration of radiolabeled pamidronate in rats, approximately 50% of the compound was rapidly adsorbed by bone and slowly eliminated from the body through 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 of parathyroid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return toward normal. Phosphate therapy was administered in 30% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned toward normal within 7-10 days.

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

Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in metastatic bone disease and hypercalcemia of malignancy. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Correction of excessive bone resorption and adequate fluid administration to correct volume deficits are therefore essential to the management of hypercalcemia.

Most cases of hypercalcemia associated with malignancy occur in patients who have breast cancer; squamous-cell tumors of the lung or head and neck; renal-cell carcinoma; and certain hematologic malignancies, such as multiple myeloma and some types of lymphomas. A few less-common malignancies, including vasoactive intestinal-peptide-producing tumors and cholangiocarcinoma, have a high incidence of hypercalcemia as a metabolic complication. Patients who have hypercalcemia of malignancy can generally be divided into two groups, according to the pathophysiologic mechanism involved.

In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE AND ADMINISTRATION).

Clinical Trials

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

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

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

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

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

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

Change in Corrected Serum Calcium by Time from Initiation of Treatment

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)			P-Value ¹
	Aredia	Didronel		
Baseline	14.6	13.8		
24	-0.3	-0.5		

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 \pm SD body retention of pamidronate was calculated to be $54 \pm 16\%$ of the dose over 120 hours.

Metabolism

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

Excretion

After administration of 30, 60, and 90 mg of Aredia over 4 hours, and 90 mg of Aredia over 24 hours, an overall mean \pm SD of $46 \pm 16\%$ of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean \pm SD elimination half-life is 28 ± 7 hours. Mean \pm 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.

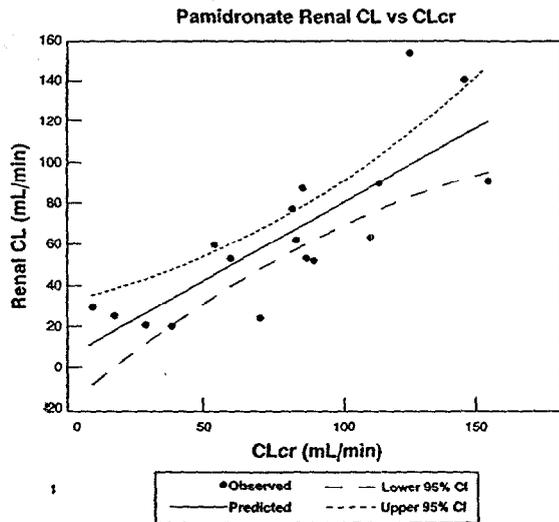
Pediatric

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.

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

Dose (infusion rate)	Maximum Concentration (ug/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%)

Excretion of calcium into the blood as urine 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 vasovascular 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 ($\geq 15\%$ decrease of corrected serum calcium from baseline), at day 14.

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

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

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

Change in Corrected Serum Calcium by Time from Initiation of Treatment

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)		P-Value ¹
	Aredia	Didronel	
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

¹Comparison 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.

Unlike Aredia 60 mg, the drug has not been investigated in a controlled clinical trial employing a 90-mg dose infused over a 4-hour period.

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

% Decrease	SAP				UOHP/C		
	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=.049).

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

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

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

382 patients receiving chemotherapy were randomized, 185 to Aredia and 197 to placebo. 372 patients receiving hormonal therapy were randomized, 182 to Aredia and 190 to placebo. All but three patients were evaluable for efficacy. Patients were followed for 24 months of therapy or until 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

Mean Change (Δ) from Baseline at Last Measurement

	Breast Cancer Patients Receiving Chemotherapy					Breast Cancer Patients Receiving Hormonal Therapy				
	Aredia		Placebo		A vs P P-Value*	Aredia		Placebo		A vs P P-Value*
	N	Mean Δ	N	Mean Δ		N	Mean Δ	N	Mean Δ	
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 ≥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).

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

PRECAUTIONS

General

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

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 25, 45, 75, 100, 150, and 300 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.

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	Breast Cancer Patients Receiving Chemotherapy						Breast Cancer Patients Receiving Hormonal Therapy					
	Any SRE		Radiation		Fractures		Any SRE		Radiation		Fractures	
N	A	P	A	P	A	P	A	P	A	P	A	P
Skeletal Morbidity Rate (#SRE/year)												
Mean	2.5	3.7	0.8	1.3	1.6	2.2	2.4	3.6	0.6	1.2	1.6	2.2
P-Value	<.001		<.001†		.018†		.021		.013†		.040†	
Proportion of patients having an SRE	46%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001†		.014†		.094		.058†		.054†	
Median Time to SRE (months)	13.9	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		.016†		.113†	

†Fractures and radiation to bone were two of several secondary endpoints. The statistical significance of these analyses may be overestimated since numerous analyses were performed. **NR = Not Reached.

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

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

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.

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

Laboratory Tests

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

Drug Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Aredia was nonmutagenic in six mutagenicity assays: Ames test, *Salmonella* and *Escherichia coli*/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.

Aredia® pamidronate disodium for Injection

Pregnancy Category C

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

Dolus intravenous studies conducted in rats and rabbits determined that Aredia produces maternal toxicity and embryofetal effects when given during organogenesis at doses of 0.6 to 8.3 times the highest recommended human dose for a single intravenous infusion. As it has been shown that Aredia can cross the placenta in rats and has produced marked maternal and nonteratogenic embryofetal effects in rats and rabbits, it should not be given to women during pregnancy.

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

Clinical Studies

Hypercalcemia of Malignancy

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

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

Symptomatic treatment resulted in rapid resolution in all patients.

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

Four of 128 patients (3%) who received Aredia during the three U.S. controlled hypercalcemia clinical studies were reported to have had seizures, 2 of whom had preexisting seizure disorders. None of the seizures were considered to be drug-related by the investigators.

However, a possible relationship between the drug and the occurrence of seizures cannot be ruled out. It should be noted that in the saline arm 1 patient (4%) had a seizure.

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				
	60 mg over 4 hr n=23	Aredia 60 mg over 24 hr n=73	90 mg over 24 hr n=17	Didronel 7.5 mg/kg x 3 days n=35	Saline 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

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	16.6	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	10.8
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
CNS						
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
Respiratory System						
Coughing	26.3	22.5	25.3	19.7	25.7	20.8
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.

Post-Marketing Experience

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

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

Hypercalcemia of Malignancy

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

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				
	60 mg over 4 hr n=23	Aredia 60 mg over 24 hr n=73	90 mg over 24 hr n=17	Didronel 7.5 mg/kg x 3 days n=35	Saline 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	4	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.

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
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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 28% 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 hypercalcemia. Another Aredia patient discontinued therapy due to severe bone pain after each infusion, which the investigator felt was trial-drug-related.

Post-Marketing Experience

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

OVERDOSAGE

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

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

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

DOSE 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. 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. The 60-mg dose is given as an initial, SINGLE-DOSE, intravenous infusion over at least 4 hours. The 90-mg dose must be given by an initial, SINGLE-DOSE, intravenous infusion over 24 hours.

Severe Hypercalcemia

The recommended dose of Aredia in severe hypercalcemia (corrected serum calcium* >13.5 mg/dL) is 90 mg. The 90-mg dose must be given by an initial, SINGLE-DOSE, intravenous infusion over 24 hours.

*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 total dose of 90 mg.

Retreatment

A limited number of patients with Paget's disease have received more than one treatment with 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 serum creatinine ≥ 3.0 mg/dL.

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

Hypercalcemia of Malignancy

The daily dose must be administered as an intravenous infusion over at least 4 hours for 60-mg dose, and over 24 hours for the 90-mg dose. 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 (36°F-46°F (2°C-8°C)) for up to 24 hours.

HOW SUPPLIED

- Vials - 30 mg - each contains 30 mg of sterile, lyophilized pamidronate disodium and 470 mg of mannitol, USP.
- Carton of 4 vials.....NDC 0083-26X
- Vials - 90 mg - each contains 90 mg of sterile, lyophilized pamidronate disodium and 375 mg of mannitol, USP.
- Carton of 1 vial.....NDC 0083-28X

Do not store above 86°F (30°C).

10

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 discoloration prior to administration, whenever solution and container permit.

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

SUPPLIED

30 mg - each contains 30 mg of sterile, lyophilized pamidronate disodium and 470 mg of mannitol, USP.
Carton of 4 vialsNDC 0083-266
90 mg - each contains 90 mg of sterile, lyophilized pamidronate disodium and 375 mg of mannitol, USP.
Carton of 1 vialNDC 0083-266

Do not store above 86°F (30°C).

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 **NOVARTIS**

 Novartis Pharmaceuticals Corporation
Hanover, New Jersey 07936

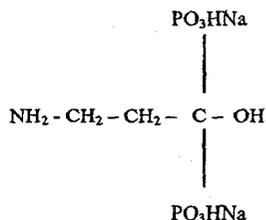
PROPOSED LABELING

Pamidronate Disodium Injection

For Intravenous Infusion

DESCRIPTION:

Pamidronate Disodium Injection is a bone-resorption inhibitor available in 30 mg or 90 mg vials for intravenous administration. Each mL of the 30 mg vial contains: 3 mg Pamidronate Disodium; 47 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. Each mL of the 90 mg vial contains: 9 mg Pamidronate Disodium, 37.5 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. The pH of a 1% solution of pamidronate disodium in distilled water is approximately 8.3. Pamidronate disodium, is 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, 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 $\text{C}_3\text{H}_9\text{NO}_7\text{P}_2\text{Na}_2$ and its molecular weight is 279.1.

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

CLINICAL PHARMACOLOGY:

The principal pharmacologic action of pamidronate disodium is inhibition of bone resorption. Although the mechanism of antiresorptive action is not completely understood, several factors are thought to contribute to this action. Pamidronate disodium 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, pamidronate disodium inhibits bone resorption apparently without inhibiting bone formation and mineralization. Of relevance to the treatment of hypercalcemia of malignancy is the finding that pamidronate disodium 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 pamidronate disodium over 4 hours and 90 mg of pamidronate disodium over 24 hours (Table 1).

Distribution

The mean \pm SD body retention of pamidronate was calculated to be $54 \pm 16\%$ 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 pamidronate disodium over 24 hours, an overall mean \pm SD of $46 \pm 16\%$ of the drug was excreted unchanged in the urine within 120 hours. Cumulative urinary excretion was linearly related to dose. The mean \pm SD elimination half-life is 28 ± 7 hours. Mean \pm 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.

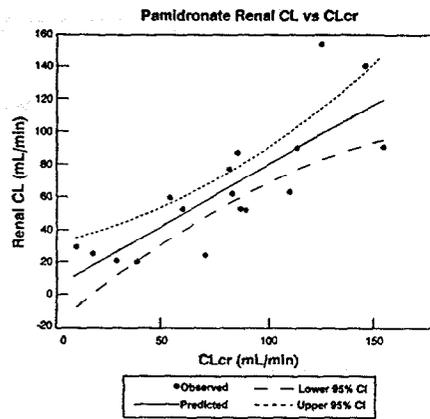
Pediatric

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 pamidronate disodium 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 pamidronate disodium 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 pharmacokinetic data for pamidronate disodium in patients who have hepatic insufficiency.

Drug-Drug Interactions

There are no human pharmacokinetic data for drug interactions with pamidronate disodium.

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

Dose (infusion Rate)	Maximum Concentration (mcg/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% to 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 pamidronate disodium, 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 to 48 hours. Studies in rats injected with radiolabeled pamidronate disodium 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 to 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 pamidronate disodium, 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 to 10 days.

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

Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in metastatic bone disease and hypercalcemia of malignancy. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Correction of excessive bone resorption and adequate fluid administration to correct volume deficits are therefore essential to the management of hypercalcemia.

Most cases of hypercalcemia associated with malignancy occur in patients who have breast cancer; squamous-cell tumors of the lung or head and neck; renal-cell carcinoma; and certain hematologic malignancies, such as multiple myeloma and some types of lymphomas. A few less-common malignancies, including vasoactive intestinal-peptide-producing tumors and cholangiocarcinoma, have a high incidence of hypercalcemia as a metabolic complication. Patients who have hypercalcemia of malignancy can generally be divided into two groups, according to the pathophysiologic mechanism involved.

In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see **DOSE 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 Pamidronate Disodium Injection as a single 24-hour intravenous infusion if their corrected serum 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 Pamidronate Disodium Injection were significantly reduced from baseline in all three dosage groups. As a result, by 7 days after initiation of treatment with Pamidronate Disodium Injection, 40%, 61%, and 100% of the patients receiving 30 mg, 60 mg, and 90 mg of Pamidronate Disodium Injection, respectively, had normal-corrected serum calcium levels. Many patients (33% to 53%) in the 60-mg and 90-mg dosage groups continued to have normal-corrected serum calcium levels, or a partial response ($\geq 15\%$ decrease of corrected serum calcium from baseline), at day 14.

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

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

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

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

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)			P-Value ¹
	Pamidronate Disodium Injection	Didronel		
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

¹Comparison 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 Pamidronate Disodium Injection 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 Pamidronate Disodium Injection 60-mg 4-hour infusion, Pamidronate Disodium Injection 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 Pamidronate Disodium Injection 60-mg 4-hour infusion group and 26% of the patients in the Pamidronate Disodium Injection 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 Pamidronate Disodium Injection 60-mg 4-hour infusion and Pamidronate Disodium Injection 60-mg 24-hour infusion, respectively.

In all three trials, patients treated with Pamidronate Disodium Injection 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 Pamidronate Disodium Injection 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.

Unlike Pamidronate Disodium Injection 60 mg, the drug has not been investigated in a controlled clinical trial employing a 90-mg dose infused over a 4-hour period.

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 Pamidronate Disodium Injection as a single 4-hour infusion on 3 consecutive days, for total doses of 15 mg, 45 mg, and 90 mg of Pamidronate Disodium Injection.

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 Pamidronate Disodium Injection on serum alkaline phosphatase (SAP) and urine hydroxyproline/creatinine ratios (UOHP/C) are summarized in the following table:

% Decrease	SAP			UOHP/C		
	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 Pamidronate Disodium Injection. 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 can 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 Pamidronate Disodium Injection or placebo in addition to their underlying antimyeloma therapy to determine the effect of Pamidronate Disodium Injection 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 Pamidronate Disodium Injection or placebo as a monthly 4-hour intravenous infusion for 9 months. Of the 392 patients, 377 were evaluable for efficacy (196 Pamidronate Disodium Injection, 181 placebo). The proportion of patients developing any SRE was significantly smaller in the Pamidronate Disodium Injection group (24% vs 41%, P<0.001), and the mean skeletal morbidity rate (#SRE/year) was significantly smaller for Pamidronate Disodium Injection 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 than in the Pamidronate Disodium Injection group (P=.001, .006, and .046, respectively). Moreover, fewer Pamidronate Disodium Injection patients suffered any pathologic fracture (17% vs 30%, P=.004) or needed radiation to bone (14% vs 22%, P=.049).

In addition, decreases in pain scores from baseline occurred at the last measurement for those Pamidronate Disodium Injection 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 Pamidronate Disodium Injection-treated patients.*

After 21 months, the proportion of patients experiencing any skeletal event remained significantly smaller in the Pamidronate Disodium Injection group than the placebo group (P=.015). In addition, the mean skeletal morbidity rate (#SRE/year) was 1.3 vs 2.2 for Pamidronate Disodium Injection patients vs placebo patients (P=.008), and time to first SRE was significantly longer in the Pamidronate Disodium Injection group compared to placebo (P=.016). Fewer Pamidronate Disodium Injection 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 Pamidronate Disodium Injection 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 Pamidronate Disodium Injection and 197 to placebo. 372 patients receiving hormonal therapy were randomized, 182 to Pamidronate Disodium Injection 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 Pamidronate Disodium Injection 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	
	PDI	P	PDI	P	PDI	P	PDI	P	PDI	P	PDI	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	1.6	2.2
P-Value	<.001		<.001 [†]		.018 [†]		.021		.013 [†]		.040 [†]	
Proportion of patients having an SRE	46%	65%	28%	45%	36%	49%	55%	63%	31%	40%	45%	55%
P-Value	<.001		<.001 [†]		<.014 [†]		.094		.058 [†]		.054 [†]	
Median Time to SRE (months)	13.9	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		.016 [†]		.113 [†]	

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

**NR = Not Reached.

Bone lesion response was radiographically assessed at baseline and at 3, 6, and 12 months. The complete + partial response was 33% in Pamidronate Disodium Injection patients and 18% in placebo patients treated with chemotherapy (P=.001). No difference was seen between Pamidronate Disodium Injection 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				
	Pamidronate Disodium Injection		Placebo		PDI vs P	Pamidronate Disodium Injection		Placebo		PDI 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

Pamidronate Disodium Injection, 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 Pamidronate Disodium Injection. 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 Pamidronate Disodium Injection in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

Paget's Disease

Pamidronate Disodium Injection is indicated for the treatment of patients with moderate to severe Paget's disease of bone. The effectiveness of Pamidronate Disodium Injection was demonstrated primarily in patients with serum alkaline phosphatase ≥ 3 times the upper limit of normal. Pamidronate Disodium Injection therapy in patients with Paget's disease has been effective in reducing serum alkaline phosphatase and urinary hydroxyproline levels by $\geq 50\%$ in at least 50% of patients, and by $\geq 30\%$ in at least 80% of patients. Pamidronate Disodium Injection 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

Pamidronate Disodium Injection 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 Pamidronate Disodium Injection treatment effect appeared to be smaller in the study of breast cancer patients receiving hormonal therapy than in the study of those receiving chemotherapy, however, overall evidence of clinical benefit has been demonstrated (see **CLINICAL PHARMACOLOGY, Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma, Clinical Trials** section).

CONTRAINDICATIONS:

Pamidronate Disodium Injection is contraindicated in patients with clinically significant hypersensitivity to Pamidronate Disodium Injection or other bisphosphonates.

WARNINGS:

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

Two 7-day intravenous infusion studies were conducted in the dog wherein Pamidronate Disodium Injection was given for 1, 4, or 24 hours at doses of 1 to 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 at doses of ≥ 10 mg/kg. In the second study, slight renal tubular necrosis was observed in 1 male at 1 mg/kg when infused for 4 hours. Additional findings included elevated BUN levels in several treated animals and renal tubular dilation and/or inflammation at ≥ 1 mg/kg after each infusion time.

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

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

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

PRECAUTIONS:

General

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium, and potassium, should be carefully monitored following initiation of therapy with Pamidronate Disodium Injection. Cases of asymptomatic hypophosphatemia (12%), hypokalemia (7%), hypomagnesemia (11%), and hypocalcemia (5%-12%), were reported in Pamidronate Disodium Injection-treated patients. Rare cases of symptomatic hypocalcemia (including tetany) have been reported in association with Pamidronate Disodium Injection 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 Pamidronate Disodium Injection showed serum calcium levels below 8 mg/dL.

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

Laboratory Tests

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

Drug Interactions

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

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 pamidronate disodium 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. Pamidronate disodium (daily oral administration) was not carcinogenic in an 80-week study in mice.

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

Pregnancy Category C

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

Bolus intravenous studies conducted in rats and rabbits determined that Pamidronate Disodium Injection 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 Pamidronate Disodium Injection can cross the placenta in rats and has produced marked maternal and nonteratogenic embryo/fetal effects in rats and rabbits, it should not be given to women during pregnancy.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness of Pamidronate Disodium Injection 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 Pamidronate Disodium Injection in 34% of patients in clinical trials. In the saline trial, 18% of patients had a temperature elevation of at least 1°C 24 to 48 hours after treatment.

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

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

Four of 128 patients (3%) who received Pamidronate Disodium Injection during the three U.S. controlled hypercalcemia clinical studies were reported to have seizures, 2 of whom had preexisting seizure disorders. None of the seizures were considered to be drug-related by the investigators. However, a possible relationship between the drug and the occurrence of seizures cannot be ruled out. It should be noted that in the saline arm 1 patient (4%) had a seizure.

At least 15% of patients treated with Pamidronate Disodium Injection 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 the comparative, controlled U.S. trials.

Treatment-Related Adverse Experiences Reported in Three U.S. Controlled Clinical Trials

	Percent of Patients				Saline n=23
	Pamidronate Disodium Injection			Didronel	
	60 mg over 4 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	
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
Diarhea	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 $>1^{\circ}\text{C}$ above pretreatment baseline was noted within 48 hours after completion of treatment in 21% of the patients treated with 90 mg of Pamidronate Disodium Injection in clinical trials.

Drug-related musculoskeletal pain and nervous systems (dizziness, headache, paresthesia, increased sweating) were more common in patients with Paget's disease treated with 90 mg of Pamidronate Disodium Injection 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 Pamidronate Disodium Injection in two U.S. clinical trials, were fever, nausea, back pain, and bone pain.

At least 10% of all Pamidronate Disodium Injection-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 Pamidronate Disodium Injection 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

	Pamidronate Disodium Injection 90 mg over 4 hrs N=205		Pamidronate Disodium Injection 90 mg over 2 hours N=367		All Pamidronate Disodium Injection 90 mg N=572	
	Placebo N=187	Placebo N=386	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	16.6	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	10.8
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
CNS						
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
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 Pamidronate Disodium Injection 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 Pamidronate Disodium Injection patients and 12.3% of placebo patients. Mineral and electrolyte disturbances, including hypocalcemia, were reported rarely and in similar percentages of Pamidronate Disodium Injection-treated patients compared with those in the placebo group. The reported frequencies of hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia for Pamidronate Disodium Injection-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 Pamidronate Disodium Injection (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 Pamidronate Disodium Injection group than in the placebo group (13.6% and 26% vs 10.8% and 20.1%, respectively).

In multiple myeloma patients, there were five Pamidronate Disodium Injection-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 Pamidronate Disodium Injection-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 Pamidronate Disodium Injection-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 Pamidronate Disodium Injection patient discontinued the trial due to severe bone pain after each infusion, which the investigator felt was trial-drug-related.

Post-Marketing Experience

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

OVERDOSAGE:

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

In addition, one obese woman (95 kg) who was treated with 285 mg of Pamidronate Disodium Injection/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 Pamidronate Disodium Injection in moderate hypercalcemia (corrected serum calcium* of approximately 12 to 13.5 mg/dL) is 60 to 90 mg. The 60-mg dose is given as an initial, SINGLE-DOSE, intravenous infusion over at least 4 hours. The 90-mg dose must be given by an initial, SINGLE-DOSE, intravenous infusion over 24 hours.

Severe Hypercalcemia

The recommended dose of Pamidronate Disodium Injection in severe hypercalcemia (corrected serum calcium* > 13.5 mg/dL) is 90 mg. The 90-mg dose must be given by an initial, SINGLE-DOSE, intravenous infusion over 24 hours.

*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 Pamidronate Disodium Injection for hypercalcemia. Retreatment with Pamidronate Disodium Injection, 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 Pamidronate Disodium Injection 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 Pamidronate Disodium Injection 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 Pamidronate Disodium Injection 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 pamidronate disodium infusion.

Limited information is available on the use of Pamidronate Disodium Injection in multiple myeloma patients with a serum creatinine ≥ 3.0 mg/dL.

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

Osteolytic Bone Metastases of Breast Cancer

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

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

Preparation of Infusion

Hypercalcemia of Malignancy

The daily dose must be administered as an intravenous infusion over at least 4 hours for the 60-mg dose, and over 24 hours for the 90-mg dose. The recommended dose should be diluted in 1000 mL of sterile 0.45% or 0.9% Sodium Chloride Injection, 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 Injection, 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 Injection, USP, or 5% Dextrose Injection, USP, and administered over a 2-hour period every 3 to 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 Injection, USP, or 5% Dextrose Injection, USP, and administered over a 4-hour period on a monthly basis.

Pamidronate Disodium Injection 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.

HOW SUPPLIED:

NDC No.	Product No.	
730410	63323-734-10	Pamidronate Disodium Injection, 30 mg/vial (3 mg/mL), in a 10 mL vial
730510	63323-735-10	Pamidronate Disodium Injection, 90 mg/vial (9 mg/mL), in a 10 mL vial

Store at controlled room temperature 15°– 30°C (59° – 86°F).

**PAMIDRONATE
DISODIUM**

INJECTION

30 mg/vial

(3 mg/mL)

For Intravenous
Infusion

Do not mix with
calcium-containing
infusion solutions.

10 mL Vial

N 63323-734-10

Sterile, Nonpyrogenic

730410

Each mL contains: 3 mg Pamidronate Disodium; 47 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. The pH of the solution is 6.0 to 7.4.

Usual Dosage: See insert.

MUST BE DILUTED PRIOR TO ADMINISTRATION.

Rx only

401908

LOT

EXP

**PAMIDRONATE
DISODIUM**

INJECTION

90 mg/vial
(9 mg/mL)

For Intravenous
Infusion

Do not mix with
calcium- containing
infusion solutions.

10 mL Vial

N 63323-735-10

Sterile, Nonpyrogenic

730510

Each mL contains: 9 mg Pamidronate Disodium; 37.5 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. The pH of the solution is 6.0 to 7.4.

Usual Dosage: See insert.

MUST BE DILUTED PRIOR TO ADMINISTRATION.

Rx only

401909

LOT

EXP

**PAMIDRONATE
DISODIUM**

INJECTION

30 mg/vial

(3 mg/mL)

For Intravenous
Infusion

Do not mix with
calcium-containing
infusion solutions.

10 mL Vial

N 63323-734-10

Sterile, Nonpyrogenic

730410

Each mL contains: 3 mg Pamidronate Disodium; 47 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. The pH of the solution is 6.0 to 7.4.

Usual Dosage: See insert.

MUST BE DILUTED PRIOR TO ADMINISTRATION.

Rx only

401908

LOT

EXP

PAMIDRONATE

DISODIUM

INJECTION

90 mg/vial

(9 mg/mL)

For Intravenous
Infusion

Do not mix with
calcium- containing
infusion solutions.

10 mL Vial

N 63323-735-10

Sterile, Nonpyrogenic

730510

Each mL contains: 9 mg Pamidronate Disodium; 37.5 mg Mannitol, USP; Water for Injection, USP, q.s.; Phosphoric acid to adjust pH. The pH of the solution is 6.0 to 7.4.

Usual Dosage: See insert.

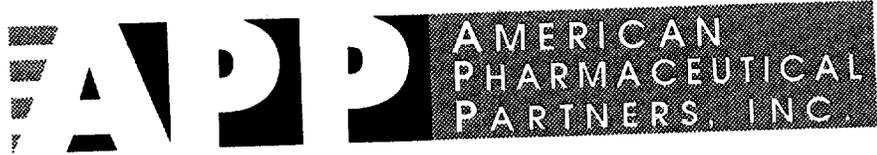
MUST BE DILUTED PRIOR TO ADMINISTRATION.

Rx only

401909

LOT

EXP



ATTACHMENT 2

Table 3. Number of all-listed diagnoses for discharges from short-stay hospitals, by ICD-9-CM code, sex and age of patient, and geographic region of hospital: United States, 1996—Con.

Excludes discharges of inpatients from non-Federal hospitals. Excludes newborn infants. Code numbers are from the *International Classification of Diseases, 9th Revision, 1st Modification (ICD-9-CM)*. Totals include data for categories not listed in table; see Methods section]

ICD-9-CM code	Total	Sex		Age				Region			
		Male	Female	Under 15 years	15-44 years	45-64 years	65 years and over	Northeast	Midwest	South	West
Number of all-listed diagnoses in thousands											
272	1,023	526	496	*	114	428	479	241	275	313	194
272.0	572	284	288	*	63	252	257	166	149	165	93
272.1	33	17	16	*	*6	16	11	*	*6	16	*6
272.2	17	*9	*8	*	*	*7	*7	*	*	*6	*5
272.4	379	206	174	*	36	145	198	62	113	120	85
272.9	10	*5	*	*	*	*	*	*	*	*	*
273	55	26	29	*	10	11	30	11	15	21	*7
273.1	*9	*5	*	-	*	*	*8	*	*	*	*
273.8	39	18	21	*	9	*8	18	*5	13	16	*5
274	174	117	57	-	9	40	125	44	43	53	34
274.0	54	35	19	-	*	10	40	12	14	16	12
274.9	117	81	37	-	*	29	84	31	29	36	21
275	204	94	110	*6	47	55	96	43	49	78	34
275.0	*7	*	*	*	*	*	*	*	*	*	*
275.2	69	30	39	*	17	18	33	16	18	27	*8
275.3	37	19	18	*	11	11	13	*5	*6	17	*8
275.4	90	39	51	*	18	24	47	20	21	33	16
276	4,042	1,635	2,407	387	656	747	2,252	746	1,128	1,512	657
276.0	94	37	57	*7	11	13	63	15	27	35	17
276.1	759	322	437	25	94	159	481	123	225	287	124
276.2	155	75	80	22	26	34	73	30	46	49	30
276.3	38	17	21	*	*7	*8	19	*	12	17	*
276.4	19	*8	11	*	*	*5	10	*	*6	*7	*
276.5	1,791	713	1,078	287	311	244	950	352	465	696	278
276.6	61	29	32	*	10	21	28	*8	13	23	18
276.7	242	128	114	10	35	52	145	43	67	83	48
276.8	776	264	513	22	146	192	417	155	225	273	123
276.9	106	42	64	*8	15	17	66	11	42	42	12
277	45	27	18	14	18	*6	*6	15	14	10	*7
277.0	25	15	11	11	14	*	*	*9	*9	*6	*
277.00	25	15	11	11	14	*	*	*9	*9	*6	*
278	567	190	377	*6	162	247	151	108	167	190	101
278.0	556	186	370	*6	159	241	150	105	165	186	99
278.00	429	151	277	*6	111	186	125	84	129	138	78
278.01	127	35	92	*	47	55	25	21	36	48	22
278.8	*5	*	*	*	*	*	*	*	*	*	*
279	19	*8	11	*	*7	*	*	*	*	*	*6
279.0	10	*	*6	*	*	*	*	*	*	*	*
30-289	3,921	1,536	2,385	179	954	815	1,972	839	915	1,417	750
280	583	200	383	19	130	119	314	117	136	228	102
280.0	356	128	228	*	76	79	199	71	78	144	63
280.8	*7	*	*6	*	*	*	*	*	*	*	*
280.9	217	70	147	15	52	40	111	44	56	81	36
281	107	40	67	*	11	18	78	22	25	46	15
281.0	37	12	25	*	*	*	32	10	10	16	*
281.1	10	*	*6	-	*	*	*9	*	*	*	*
281.9	51	20	31	*	*8	10	33	*8	11	22	10
282	130	53	76	29	77	11	13	36	31	46	16
282.4	18	*5	13	*	*6	*	*6	*5	*	*	*
282.5	18	*	14	*	13	*	*	*	*	10	*
282.6	83	39	44	22	55	*	*	24	22	29	*8
282.60	18	*8	10	*7	*8	*	*	*	*	*8	*
282.61	*5	*	*	*	*	*	-	*	*	*	*
282.69	59	27	31	10	46	*	*	18	15	21	*5

* Figure does not meet standard of reliability or precision.
- Quantity zero.

NOTE: Estimates of 5,000-9,000 are to be used with caution; see Methods section.

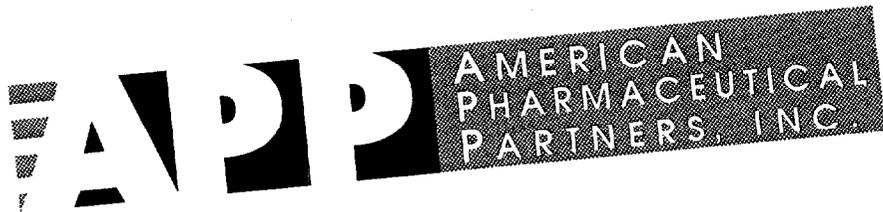
Table 3. Number of all-listed diagnoses for discharges from short-stay hospitals, by ICD-9-CM code, sex and age of patient, and geographic region of hospital: United States, 1996—Con.

[Discharges of inpatients from non-Federal hospitals. Excludes newborn infants. Code numbers are from the *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)*. Totals include data for categories not listed in table; see *Methods* section]

ICD-9-CM code	Total	Sex		Age				Region			
		Male	Female	Under 15 years	15-44 years	45-64 years	65 years and over	Northeast	Midwest	South	West
Number of all-listed diagnoses in thousands											
726.65	*6	*5	*	*	*	*	*	*	*	*	*
726.7	*5	*	*	*	*	*	*	*	*	*	*
726.9	*8	*6	*	*	*	*	*	*	*	*	*
726.91	*6	*	*	—	*	*	*	*	*	*	*
727	60	25	35	*	22	18	17	16	12	17	15
727.0	32	13	18	*	13	10	*7	*9	*8	10	*5
727.00	13	*6	*8	*	*	*	*	*	*	*	*
727.05	10	*	*5	*	*6	*	*	*	*	*	*
727.4	*7	*	*	—	*	*	*	*	*	*	*
727.8	*8	*	*	*	*	*	*	*	*	*	*
728	81	40	40	*	23	23	32	23	14	27	16
728.8	52	26	25	*	17	17	16	15	*8	15	14
728.85	14	*6	*8	*	*6	*	*	*	*	*	*6
728.86	*6	*	*	—	*	*	*	*	*	*	*
728.89	28	16	12	*	*9	*8	11	9	*5	*7	*6
728.9	11	*7	*	*	*	*	*6	*	*	*	*
729	166	54	113	*	47	53	65	27	49	54	35
729.1	54	10	44	*	21	20	13	10	17	18	9
729.2	10	*	*7	—	*	*	*	*	*	*	*
729.5	46	18	29	*	13	15	18	*9	17	11	10
729.8	48	20	28	*	*8	12	28	*7	13	19	10
729.81	*8	*	*5	*	*	*	*	*	*	*	*
729.82	*7	*	*	—	*	*	*	*	*	*	*
729.89	34	16	18	*	*	*7	22	*5	*8	13	*8
730	111	59	52	*	22	33	52	28	25	38	20
730.0	33	20	14	*	*6	10	15	10	*7	10	*6
730.07	17	11	*6	*	*	*7	*8	*6	*	*5	*
730.08	*5	*	*	*	*	*	*	*	*	*	*
730.1	26	13	14	*	*6	*6	13	*7	*7	*8	*5
730.15	*6	*	*	*	*	*	*	*	*	*	*
730.17	*9	*	*	*	*	*	*	*	*	*	*
730.18	*6	*	*	*	*	*	*	*	*	*	*
730.2	47	22	25	*	*8	15	22	11	10	18	*9
730.26	*6	*	*	*	*	*	*	*	*	*	*
730.27	23	10	13	*	*	*7	13	*	*6	*9	*
730.28	*8	*	*	*	*	*	*	*	*	*	*
731	36	20	16	—	*	*7	27	9	12	11	*
* 731.0 P.A.S.E.T.'S	19	9	10	—	—	*	18	*6	*7	*	*
731.8	17	11	*6	—	*	*6	9	*	*	*7	*
732	11	*6	*	*7	*	*	*	*	*	*	*
733	641	127	514	*	57	93	488	122	149	245	125
733.0	297	33	265	*	*	22	272	54	71	112	60
733.00	264	30	234	*	*	18	244	48	65	103	48
733.01	20	*	18	—	—	*	19	*	*	*	*9
733.09	12	*	11	*	*	*	*8	*	*	*	*
733.1	182	36	145	*	*7	21	153	34	40	72	35
733.10	*5	*	*	—	*	*	*	*	*	*	*
733.11	*5	*	*	—	*	*	*	*	*	*	*
733.13	116	25	92	*	*	11	103	23	28	47	18
733.14	18	*	14	*	*	*	13	*	*	*6	*
733.15	11	*	*9	*	*	*	*8	*	*	*	*
733.19	22	*	18	*	*	*	19	*	*	9	*6
733.4	46	20	26	*	14	16	16	*9	10	20	*7
733.42	35	15	19	*	10	13	12	*6	*6	18	*
733.49	*6	*	*	*	*	*	*	*	*	*	*

* Figure does not meet standard of reliability or precision.
 — Quantity zero.

NOTE: Estimates of 5,000-9,000 are to be used with caution; see *Methods* section.



ATTACHMENT 3

Electrophoretic analysis of components of the serum proteins per-
 mitted determination of the amount of immunoglobulin in the serum
 (Fig. 114-2). The variety of immunoglobulins move heterogeneously
 in an electric field and form a broad peak in the gamma region.
 The immunoglobulin region of the electrophoretic pattern is usually
 normal in the sera of patients and animals with plasma cell tumors.
 A sharp spike in this region called an *M component* (M for monoclonal)
 is seen. Less commonly, the M component may appear in the alpha
 or beta globulin region. The antibody must be present at a
 concentration of at least 5 g/L (0.5 g/dL) to be detectable by this
 method. This corresponds to approximately 10^9 cells producing the
 antibody. Confirmation that such an M component is truly monoclonal
 is made by the use of immunoelectrophoresis that shows a single light and
 heavy chain type. Hence immunoelectrophoresis and electrophoresis
 permit qualitative and quantitative assessment of the M component,
 respectively. Once the presence of an M component has been con-
 firmed, electrophoresis provides the more practical information for
 patients with monoclonal gammopathies. In a given patient,
 the amount of M component in the serum is a reliable measure of the
 tumor. This makes the M component an excellent tumor marker,
 although not specific enough to be used to screen asymptomatic patients.
 In addition to the plasma cell disorders, M components may be detected
 in lymphoid neoplasms such as chronic lymphocytic leukemia
 and lymphomas of B or T cell origin; nonlymphoid neoplasms such
 as acute myelogenous leukemia, breast and colon cancer; a variety
 of neoplastic conditions such as cirrhosis, sarcoidosis, parasitic
 diseases, Gaucher's disease, and pyoderma gangrenosum; and a num-
 ber of autoimmune conditions, including rheumatoid arthritis, myas-
 tic gravis, and cold agglutinin disease. A very rare skin disease
 called lichen myxedematosus or papular mucinosis is associated
 with monoclonal gammopathy. Highly cationic IgG λ is deposited
 in the dermis of patients with this disease. It is unclear whether this
 specificity reflects the specificity of the antibody for some anti-
 body component of the dermis.

The nature of the M component is variable in plasma cell disorders.
 It may be an intact antibody molecule of any heavy chain subclass,
 or it may be an altered antibody or fragment. Isolated light or heavy
 chains may be produced. In some plasma cell tumors such as extramedul-
 lary solitary bone plasmacytomas, less than a third of patients
 have an M component. In about 20 percent of myelomas, only
 light chains are produced and in most cases are secreted in the urine

as Bence Jones proteins. The frequency of myelomas of a particular
 heavy chain class is roughly proportional to the serum concentration,
 and therefore IgG myelomas are more common than IgA and IgD
 myelomas.

MULTIPLE MYELOMA Definition Multiple myeloma repre-
 sents a malignant proliferation of plasma cells derived from a single
 clone. The terms *multiple myeloma* and *myeloma* may be used inter-
 changeably. The tumor, its products, and the host response to it result
 in a number of organ dysfunctions and symptoms of bone pain or
 fracture, renal failure, susceptibility to infection, anemia, hypercalce-
 mia, and occasionally clotting abnormalities, neurologic symptoms,
 and vascular manifestations of hyperviscosity.

Etiology The cause of myeloma is not known. Myeloma oc-
 curred with increased frequency in those exposed to the radiation of
 nuclear warheads in World War II after a 20-year latency. In contrast
 to most other B cell tumors, consistent chromosomal alterations have
 not been found in patients with myeloma, though cytogenetic abnor-
 malities are noted in a substantial fraction of cases. Overexpression
 of *myc* or *ras* genes has been noted in some cases. Mutations in
 p53 and Rb-1 have also been described, but no common molecular
 pathogenesis has yet emerged. The murine plasmacytoma models sug-
 gest that the induction of plasmacytomas (e.g., with mineral oil injec-
 tion) may require exposure to foreign antigens as well as a cellular
 event. Thus chronic antigenic stimulation may play a role in the
 transformation of a particular B cell clone. This is supported by evi-
 dence that M proteins from different persons sometimes share idio-
 types. There is also some evidence for a genetic predisposition to
 myeloma in humans. Myeloma has been seen more commonly than
 expected among farmers, wood workers, leather workers, and those
 exposed to petroleum products. The neoplastic event in myeloma may
 involve cells earlier in B cell differentiation than the plasma cell.
 Circulating B cells bearing surface immunoglobulin that share the
 idiotype of the M component are present in myeloma patients. It is
 possible that the malignant clone escapes normal control mechanisms
 at a pre-plasma cell stage of differentiation and the chronic exposure
 to a particular antigenic stimulus drives the cell to terminal differentia-
 tion. Interleukin (IL) 6 may play a role in driving myeloma cell
 proliferation; a large fraction of myeloma cells exposed to IL-6 in
 vitro respond by proliferating. It remains difficult to distinguish benign
 from malignant plasma cells on the basis of morphologic criteria in
 all but a few cases. (See Plate IV-27)

Incidence and Prevalence About 14,400 cases of myeloma
 were diagnosed in 1996, and 10,400 people died from the disease.
 Myeloma increases in incidence with age. The median age at diagnosis
 is 68 years. It is rare under age 40. The yearly incidence is around 4
 per 100,000 and remarkably similar in countries throughout the world.
 Males are slightly more commonly affected than females, and blacks
 have nearly twice the incidence of whites. In the age group over 25
 the incidence is 30 per 100,000. Myeloma accounts for about 1 percent
 of all malignancies in whites and 2 percent in blacks; 13 percent of
 all hematologic cancers in whites and 33 percent in blacks.

Pathogenesis and Clinical Manifestations (Table 114-1) Bone
 pain is the most common symptom in myeloma, affecting nearly 70
 percent of patients. The pain usually involves the back and ribs, and
 unlike the pain of metastatic carcinoma, which often is worse at night,
 the pain of myeloma is precipitated by movement. Persistent localized
 pain in a patient with myeloma usually signifies a pathologic fracture.
 The bone lesions of myeloma are caused by the proliferation of the
 tumor cells and the activation of osteoclasts that destroy the bone.
 The osteoclasts respond to osteoclast activating factors (OAF) made by
 the myeloma cells [OAF activity can be mediated by several cytokines,
 including IL-1, lymphotoxin, and tumor necrosis factor (TNF)]. How-
 ever, production of these factors stops following administration of
 glucocorticoids or interferon (IFN)- γ . The bone lesions are lytic in
 nature and are rarely associated with osteoblastic new bone formation;
 therefore, radioisotopic bone scanning is less useful in diagnosis than

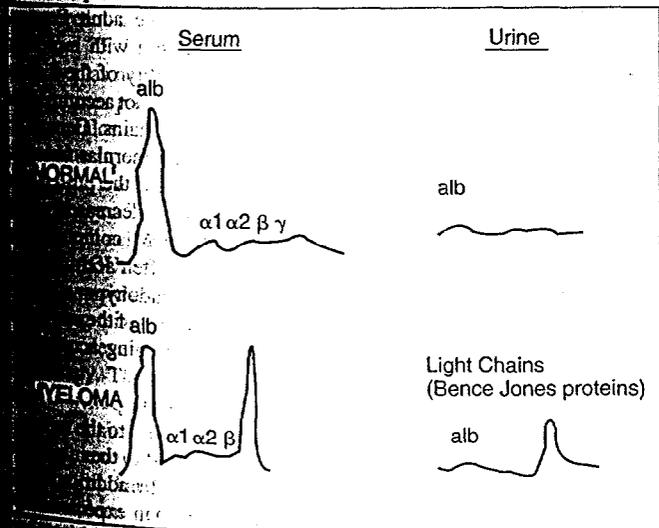
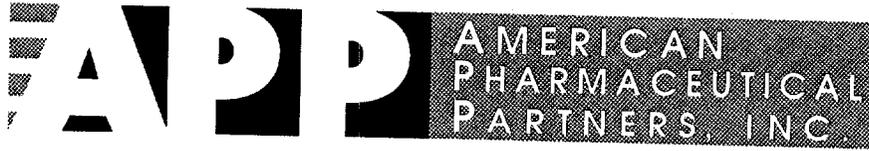


FIGURE 114-2 Representative electrophoretic patterns of serum and urine.
 This panel illustrates the normal pattern of serum and urine protein on
 electrophoresis. Since there are many different immunoglobulins in the serum,
 their different mobilities in an electric field produce a broad peak. The lower
 panel illustrates the patterns of serum and urine proteins in a patient with
 multiple myeloma. The predominance of a product of a single cell is reflected by a
 very sharp peak. The presence of free light chains in the urine is
 reflected by a sharp peak as well.



ATTACHMENT 4

HIGHLIGHTS

Incidence

- Malignancies of the bone, with an average annual incidence rate of 8.7 per million children younger than 20 years of age, comprised about 6% of childhood cancer reported by SEER areas from 1975-95.
- In the US, 650-700 children and adolescents younger than 20 years of age are diagnosed with bone tumors each year of which approximately 400 are osteosarcoma and 200 are Ewing's sarcoma.
- The two types of malignant bone cancer that predominated in children were osteosarcomas and Ewing's sarcomas, about 56% and 34% of the malignant bone tumors, respectively.
- Osteosarcomas derive from primitive bone-forming mesenchymal stem cells and most often occur near the metaphyseal portions of the long bones. The Ewing's sarcomas are believed to be of neural crest origin and occur roughly evenly between the extremities and the central axis.
- For all bone cancer combined, a steady rise in incidence rates occurred with increasing age between ages 5 and 10, and a steeper rise began at age 11 until age 15 coinciding with the adolescent growth spurt. The peak incidence of bone cancer (19 per million) occurred at age 15, after which rates showed a decline (Figure VIII.2).
- Rates did not differ much by sex among younger children, but males had higher incidence than females during adolescence (Figure VIII.4).
- For osteosarcoma, black children had a higher overall rate than did white children (Figure VIII.7). For Ewing's sarcoma the racial variation in rates was dramatic: white children had an approximate 6-fold higher incidence rate than black children (Figure VIII.8).
- The most frequent site of bone cancer development was the long bones of the lower limbs for osteosarcomas and the central axis for Ewing's sarcomas (Figure VIII.9).

Survival

- The 5-year relative survival for children with bone cancer improved from 49% in the period 1975-84, to 63% in the period 1985-94. The survival rates improved between the two time periods for both osteosarcoma (Figure VIII.11) and Ewing's sarcoma (Figure VIII.12).
- Survival rates for osteosarcoma were higher than those for Ewing's sarcoma especially in the earlier time period (Figures VIII.11 and VIII.12).

Risk factors

- Although directed ionizing radiation exposure and a few genetic susceptibility syndromes are associated with increased risk of osteosarcoma, to date no factor has emerged to explain even a modest proportion of cases (Table VIII.2). Other than the important racial difference in incidence between black and white children, no environmental factor or other characteristic has yet been shown to be a strong risk factor for Ewing's sarcoma (Table VIII.3).