NDA 20036
S-001
002
005

NDA 20-036/S-001
NDA 20-036/S-002

MAY - 6 1993

Ciba-Geigy Corporation
Attention: John R. Hanagan, M.D.
556 Morris Avenue
Summit, NJ 07901

Dear Dr. Hanagan:

Reference is made to your supplemental new drug applications submitted on December 27, 1991 (S-001), and March 26, 1992 (S-002), for Aredia (pamidronate disodium for injection).

We also acknowledge receipt of your communication dated February 5, 1993, enclosing final printed labeling as requested in our approvable letter dated August 7, 1992.

Supplement 001 provides for a 60 mg/vial dosage strength.

Supplement 002 provides for a 90 mg/vial dosage strength.

The DESCRIPTION, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections of the package insert have been modified to reflect these additions.

We have completed the review of your supplemental application and it is approved, effective the date of this letter.

The final printed labeling is being retained for our files.

Sincerely yours,

5/5/93

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

5/4/93

1,2 #101

Aredia®

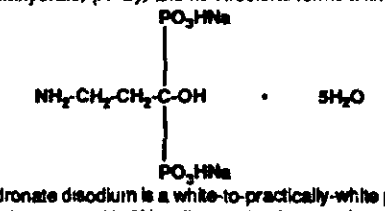
C92-48 (Rev. 10/92)

pamidronate disodium for injection
For intravenous infusion

Prescribing Information

DESCRIPTION

Aredia, pamidronate disodium, (APD), is a bone-resorption inhibitor available in 30-mg, 60-mg, or 90-mg vials for intravenous administration. Each 30-mg, 60-mg, and 90-mg vial contains, respectively, 30 mg, 60 mg, and 90 mg of sterile, lyophilized pamidronate disodium and 470 mg, 400 mg, and 375 mg of mannitol, USP. The pH of a 1% solution of pamidronate disodium in distilled water is approximately 8.3. Aredia, a member of the group of chemical compounds known as bisphosphonates, is an analog of pyrophosphate. Pamidronate disodium is designated chemically as phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, pentahydrate, (APD), and its structural formula is:



Pamidronate disodium is a white-to-practically-white powder. It is soluble in water and in 2N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is $C_3H_9NO_7P_2Na_2 \cdot 5H_2O$ and its molecular weight is 369.1.

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

CLINICAL PHARMACOLOGY

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

In cancer patients who had minimal or no bony involvement who were given an intravenous infusion of 60 mg of Aredia over 4 or 24 hours, a mean of 51% (32-80%) of the drug was excreted unchanged in the urine within 72 hours. Body retention during this period was calculated to be a mean of 49% (range 20-68%) of the dose, or 29.3 mg (12-41 mg). The urinary-excretion-rate profile after administration of 60 mg of Aredia over 4 hours exhibited biphasic disposition characteristics with an alpha half-life of 1.6 hours and a beta half-life of 27.2 hours. There are no human pharmacokinetic data for Aredia on the 90-mg dose or in patients who have either renal or hepatic insufficiency. The rate of elimination of Aredia from bone has not been determined.

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

Serum phosphate levels have been noted to decrease after administration of Aredia, presumably because of decreased release of phosphate from bone and increased renal excretion as parathyroid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return towards normal. Phosphate therapy was administered in 30% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned towards 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, 13.6 mg/dL and 13.3 mg/dL, respectively.

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

In a second double-blind, controlled clinical trial, 65 cancer patients who had corrected serum calcium levels of ≥12.0 mg/dL after at least 24 hours of saline hydration were randomized to receive either 60 mg of Aredia as a single 24-hour intravenous infusion or 7.5 mg/kg of 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 patients in the Didronel group had normal corrected serum calcium levels ($P < 0.05$). When partial responders (≥15% decrease of serum calcium from baseline) were also included, the response rates were 97% for the Aredia group and 65% for the 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 13% 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)		
	Aredia	Didronel	p Value[1]
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

[1] Comparison between treatment groups

In both 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.

Twenty-five patients who had recurrent or refractory hypercalcemia of malignancy were given a second course of 60 mg of Aredia. Of these, 40% showed a complete response and 20% 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 treatment.

INDICATIONS AND USAGE

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.

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 administration of Aredia. A 3-month study in rats found cortical tubular changes including epithelial degeneration with intravenous doses ≥ 5 mg/kg, given once every two weeks. Following a recovery period (1 month), the degenerative changes were completely reversed. Focal fibrosis of renal tubules was partially reversed.

In two studies conducted in dogs, Aredia was given as a bolus intravenous injection either daily for 1 month or once a week for 3 months. In the 1-month study, tubulointerstitial nephritis, tubular degeneration and dilation occurred at 2 mg/kg. At recovery (1

month) the severity of these lesions was minimal or trace. Similar lesions (slight to marked severity) were noted in the 3-month study at 3 mg/kg and higher. However, no improvement of the lesions was observed following the 1-month recovery period.

Patients with hypercalcemia 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 enamel formation with single-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 (16%), hypokalemia (9%), hypomagnesemia (12%), and hypocalcemia (6-12%), 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.

Aredia has not been tested in patients who have class Dc renal impairment (creatinine >5.0 mg/dL). Clinical judgement should determine whether the potential benefit outweighs the potential risk in such patients.

Laboratory Tests

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

Drug Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Aredia was nonmutagenic in four mutagenicity assays: Ames test, nucleus-anomaly test, sister-chromatid-exchange study, and point-mutation test.

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

Pregnancy Category C

Aredia has been shown to increase the length of gestation and parturition in rats resulting in an increase in pup mortality when given orally at daily doses of 60 and 150 mg/kg/day from before pregnancy until after parturition. When corrected for oral bioavailability, each daily dose is approximately 0.7 to 1.7 times the highest recommended human dose for a single intravenous infusion. Oral doses of 25 to 150 mg/kg/day during the period of gestation failed to demonstrate any teratogenic, fetotoxic, or embryotoxic effects in rats or rabbits. Animal reproduction studies have not been conducted with intravenously administered Aredia. It is not known if intravenous Aredia can cause fetal harm when administered to pregnant women or if it can affect reproduction capacity. There are no adequate and well-controlled studies in pregnant women. Aredia should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 children have not been established.

ADVERSE REACTIONS

Transient mild elevation of temperature by at least 1° was noted 24-48 hours after administration of Aredia in 27% of the patients in clinical trials.

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.

Uveitis was reported in 1 patient who had hypercalcemia of malignancy; another patient who had Paget's disease of bone developed mild iritis that was responsive to indomethacin and topical steroid. Both of these patients received Aredia in uncontrolled studies.

Four of 82 patients (4.9%) who received Aredia during the 2 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.

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 related to treatment with bisphosphonates during comparative, controlled U.S. trials.

Bisphosphonate-Related Adverse Experiences in Two U.S. Controlled Clinical Trials

	Percent of Patients		
	Aredia (N = 67)		Didronel (N = 35)
	60 mg	90 mg	7.5 mg/kg x 3 days
General			
Fatigue	0	12	0
Fever	20	18	9
Fluid overload	0	0	6
Infusion-site reaction	6	18	0
Moniliasis	0	6	0
Gastrointestinal			
Abdominal pain	2	0	0
Anorexia	2	12	0
Constipation	0	6	3
Gastrointestinal hemorrhage	0	6	0
Nausea	0	18	6
Ulcerative stomatitis	0	0	3
Respiratory System			
Dyspnea	0	0	3
Rales	0	6	0
Rhinitis	0	6	0
Upper respiratory infection	2	0	0
CNS			
Convulsions	0	0	3
Insomnia	2	0	0
Somnolence	2	6	0
Taste perversion	0	0	3
Abnormal vision	2	0	0
Cardiovascular			
Atrial fibrillation	0	6	0
Hypertension	0	6	0
Syncope	0	6	0
Tachycardia	0	6	0
Endocrine System			
Hypothyroidism	0	6	0
Hemic and Lymphatic System			
Anemia	0	6	0
Laboratory Abnormality			
Hypocalcemia	2	12	0
Hypokalemia	4	18	0
Hypomagnesemia	8	12	3
Hypophosphatemia	14	18	3
Abnormal hepatic function	6	0	3

OVERDOSAGE

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

Consideration should be given to the severity of as well as the symptoms of hypercalcemia. The recommended dose of Aredia in moderate hypercalcemia (corrected serum calcium of approximately 12-13.5 mg/dL) is 60-90 mg, and in severe hypercalcemia (corrected serum calcium, >13.5 mg/dL), is 90 mg, given as 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).

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.

A limited number of patients have received more than one treatment with Aredia for hypercalcemia. Retreatment with Aredia may be considered if hypercalcemia recurs. 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.

Preparation of Solution

Aredia is reconstituted by adding 10 mL of Sterile Water for Injection, USP, to each vial, resulting in a solution of 30 mg/10 mL, 60 mg/10 mL, or 90 mg/10 mL. The pH of the reconstituted solution is 6.0 - 7.4. The drug should be completely dissolved before the solution is withdrawn. The daily dose must be administered as an intravenous infusion over 24 hours. 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. **Aredia must not be mixed with calcium-containing infusion solutions, such as Ringer's solution.**

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

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

HOW SUPPLIED

Vials - 30 mg - each contains 30 mg of sterile, lyophilized pamidronate disodium and 470 mg of mannitol, USP.
Carton of 4 vials.....NDC 0083-2601-04

Vials - 60 mg - each contains 60 mg of sterile, lyophilized pamidronate disodium and 400 mg of mannitol, USP.
Carton of 1 vial.....NDC 0083-2606-01

Vials - 90 mg - each contains 90 mg of sterile, lyophilized pamidronate disodium and 375 mg of mannitol, USP.
Carton of 1 vial.....NDC 0083-2609-01

Do not store above 86°F (30°C).

Caution: Federal law prohibits dispensing without prescription.

Printed in U.S.A. C92-48 (Rev. 10/92)

CIBA

Dist. by:
Ciba Pharmaceutical Company
Division of Ciba-Geigy Corporation
Summit, New Jersey 07901

G

ORIGINAL

SCF-001 (BL)
Labeling: SCS-002 (BL)
NDA No: 20-036 Rec'd. 2-8-93
Reviewed by: _____

Final Printed Labeling for Supplement S-001
NDA 20-036

Aredia ●
pamidronate disodium for injection

60 mg/vial Label, Code # 893140

NDC 0083-2606-01 FSC 8126

Aredia®
pamidronate disodium
for injection
For intravenous infusion
Sterile, Lyophilized

60 mg/vial

Do not mix with calcium-containing infusion solutions.

Mfd. by:
Ciba-Geigy Ltd.
Basle, Switzerland

Dist. by:
Ciba Pharmaceutical Co.
Div. of Ciba-Geigy Corp.
Summit, NJ 07901

C I B A

EXP
LOT
893140

Final Printed Labeling for Supplement S-001
NDA 20-036

Aredia®
pamidronate disodium for injection

60 mg/vial Carton, Code # 875100

Labeling: SUPPL-001 (12)
NDA No: 20-036 Rec'd. 2-8-93
Reviewed by: _____

ORIGINAL

NDC 0083-2606-01 FSC 8126

Aredia® 60 mg/vial

pamidronate disodium
for injection
For Intravenous
infusion

Sterile, Lyophilized

N 3 0083-2606-01 3

Mfd. by:
Ciba-Geigy Ltd.
Basle, Switzerland

Dist. by:
Ciba Pharmaceutical Co.
Div. of Ciba-Geigy Corp.
Summit, NJ 07901

875100

NDC 0083-2606-01 FSC 8126

Aredia® 60 mg/vial

pamidronate disodium
for injection
For intravenous
infusion

1 vial

Aredia is reconstituted by adding 10 mL of Sterile Water for Injection, USP, to each vial, resulting in a solution of 60 mg/10 mL. The drug should be completely dissolved before the solution is withdrawn. The daily dose must be administered as an intravenous infusion over 24 hours. 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 up to 24 hours at room temperature.

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

Do not store above 86°F (30°C).

For intravenous infusion.

Dosage: For full directions see package insert.

See side panel for lot number and expiration date.

1 2 3 4 5 6 7 8
9 10 11 12 13 14
15 16 17 18 19
20 21 22 23 24

Final Printed Labeling for Supplement S-002
NDA 20-036

SCF-001 (BL)
Labeling: SCS-002 (BL)
NDA No: 20-036 Rec'd. 2-8-93
Reviewed by: _____

Aredia ●
pamidronate disodium for injection

90 mg/vial Label, Code # 893130

ORIGINAL

NDC 0083-2609-01 FSC 8134

Aredia®
pamidronate disodium
for injection
For intravenous infusion
Sterile, Lyophilized

90 mg/vial

Do not mix with calcium-containing infusion solutions.

Mfd. by:
Ciba-Geigy Ltd.
Basle, Switzerland

Dist. by:
Ciba Pharmaceutical Co.
Div. of Ciba-Geigy Corp.
Summit, NJ 07901

C I B A

EXP
LOT

893130

Final Printed Labeling for Supplement S-002
NDA 20-036

Aredia ●
pamidronate disodium for injection

90 mg/vial Carton, Code # 679650

SCF-001 (B)
SNS-002 (B)
Labeling:
NDA No: 20-036 Rec'd. 2-8-93
Reviewed by: _____

ORIGINAL

1 Vial

pamidronate disodium
for injection
For Intravenous Infusion

Aredia® 90 mg/vial

NDC 0083-2609-01 FSC 8136

679650

Aredia is reconstituted by adding 10 mL of Sterile Water for Injection, USP, to each vial, resulting in a solution of 90 mg/10 mL. The drug should be completely dissolved before the solution is withdrawn. The daily dose must be administered as an intravenous infusion over 24 hours. 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 up to 24 hours at room temperature.

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

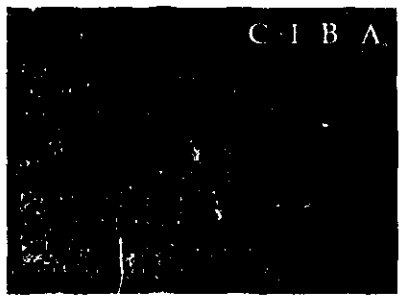
Do not store above 86°F (30°C).
For intravenous infusion.
Dosage: For full directions see package insert.
See bottom panel for lot number and expiration date.

NDC 0083-2609-01 FSC 8136

Aredia® 90 mg/vial

pamidronate disodium
for injection
For Intravenous Infusion
Sterile, Lyophilized

N 3 0083-2609-01 4



Mfd. by:
Ciba-Geigy Ltd.
Basle, Switzerland

Dist. by:
Ciba Pharmaceutical Co.
Div. of Ciba-Geigy Corp.
Summit, NJ 07901

1 2 3 4 5 6 7 8
9 10 11 12 13 14
15 16 17 18 19
20 21 22 23 24

ORIGINAL

AUG 3 1992

CHEMIST'S REVIEW

1. ORGANIZATION
DMELDP

2. NDA NUMBER
20-036

3. NAME AND ADDRESS OF APPLICANT

Ciba-Geigy Pharmaceutical Division
556 Morris Avenue
Summit, N.J. 07901

4. SUPPLEMENT NUMBER, DATE
S-002, 3-26-92

5. NAME OF DRUG
Aredia™

6. NONPROPRIETARY NAME
pamidronate disodium for injection

7. AMENDMENT #, DATE

8. SUPPLEMENT PROVIDES FOR: a new dosage strength:
90 mg lyophilized vial

9. PHARMACOLOGICAL CATEGORY
Bone reabsorption inhibitor

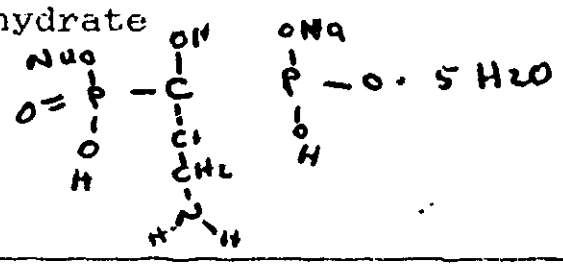
10. HOW DISPERSED
RX

11. RELATED DOCUMENTS
s-001, 12-27-91

12. DOSAGE FORM
injection

13. POTENCY
30mg, 60 mg, 90 mg

14. CHEMICAL NAME AND STRUCTURE
phosphonic acid (3-amino-1-hyoxypropyliene) bis-, disodium salt, pentahydrate



15. COMMENTS

16 CONCLUSIONS AND RECOMMENDATIONS
The supplement is approvable: issue letter requesting labels, and package insert reflecting the new dosage strength.

17. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Kathleen Hillman	Kathleen Hillman	8-3-92

DISTRIBUTION: ORIGINAL JACKET REVIEWER
DIVISION FILE
R/D initialed by: 8/3/92

NDA 20-036/S-005

JUN 9 1993

Ciba-Geigy Corporation
Attention: John R. Hanagan, M.D.
556 Morris Avenue
Summit, NJ 07901

Dear Dr. Hanagan:

Reference is made to your supplemental new drug application dated March 9, 1993, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Aredia (pamidronate disodium for injection).

The supplement provides for a revision of the ADVERSE REACTIONS section of the package-insert.

We have completed the review of your supplemental application and it is approved effective on the date of this letter.

Please submit twelve (12) copies of final printed labeling (FPL) identical to the draft labeling as soon as available. Seven of the copies should be individually mounted on heavy weight paper or similar material. The submission should be designated for administrative purposes as "FPL for Approved NDA 20-036/S-005", respectively. Approval of the submission by FDA is not required before the labeling is used. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

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

If you have any questions, please contact Mr. Randy Hedin at (301) 443-3520.

Your cooperation is appreciated.

Sincerely yours,

6/8/93

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

R Hedin
6/8/93

ORIGINAL APR - 2 1993

20-036 (S-005) Review completed: 3/31/93
Pamidronate disodium Inj.
(Aredia)
Ciba-Geigy

Review and Evaluation of Clinical Data

1. **Name of drug:** Trade: Aredia
Generic: Pamidronate disodium for injection

2. **Dosage form and route of administration:** Available in vials, each containing 30 mg of sterile lyophilized pamidronate disodium and 470 mg of mannitol, USP. The recommended dose is administered as an intravenous infusion over 24 hours after dilution in sterile Water for injection (10 ml) and 1L of sterile normal saline or 5% Dextrose Injection, USP.

3. **Category or use of drug:** For the treatment of hypercalcemia of malignancy.

4. **Reason for submission and date:** Draft package insert with a revision of the AR section. Date of submission: 3/9/1993.

5. **Summary evaluation:**

The sponsor was requested to revise the third paragraph of the Adverse Reactions section of the labeling to incorporate information regarding occurrence of ocular side effects in patients treated with Aredia (See our letter of October 9,1992).

The third paragraph of the Adverse Reactions section of the labeling has been replaced with the following: "Rare cases of uveitis, iritis, scleritis, and episcleritis have been reported, including one case of scleritis upon rechallenge."

The revised third paragraph of the Adverse Reactions section of the labeling is acceptable. The statement reflects current information regarding ocular side effects associated with Aredia therapy.

6. **Conclusion and recommendation:** The supplement (s-005) which provides a draft labeling revision to incorporate information regarding ocular side effects of Aredia is acceptable.

S.N.Dutta, M.D.

4/2/93

CC: NDA 20-036 (S-005)
HFD-340
HFD-510
HFD-510/SND/Pierce/4/2/93

Aredia® C92-57 (Rev. 1/93)

APPROVED 6.9.93

Revision of current C92-45 in accordance with FDA letter of October 9, 1992: In ADVERSE REACTIONS section, replace third paragraph to include additional information regarding ocular side effects.

Base copy: C92-45

C92-57 (Rev. 1/93)

Aredia®

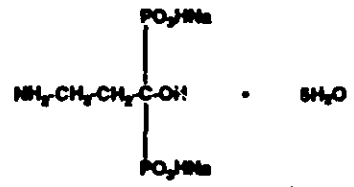
~~C92-45 (Rev. 10/92)~~
~~665951~~

pamidronate disodium for injection
For Intravenous Infusion

Prescribing Information

DESCRIPTION

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



Pamidronate disodium is a white-to-practically-white powder. It is soluble in water and in 2N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is $C_3H_9NO_7P_2Na_2 \cdot 5H_2O$ and its molecular weight is 369.1.

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

CLINICAL PHARMACOLOGY

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

In cancer patients who had minimal or no bony involvement who were given an intravenous infusion of 60 mg of Aredia over 4 or 24 hours, a mean of 51% (32-80%) of the drug was excreted unchanged in the urine within 72 hours. Body retention during this period was calculated to be a mean of 49% (range 20-68%) of the dose, or 29.3 mg (12-41 mg). The urinary-excretion-rate profile after administration of 60 mg of Aredia over 4 hours exhibited biphasic disposition characteristics with an alpha half-life of 1.6 hours and a beta half-life of 27.2 hours. There are no human pharmacokinetic data for Aredia on the 90-mg dose or in patients who have either renal or hepatic insufficiency. The rate of elimination of Aredia from bone has not been determined.

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

Serum phosphate levels have been noted to decrease after administration of Aredia, presumably because of decreased release of phosphate from bone and increased renal excretion as parathy-

roid hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return towards normal. Phosphate therapy was administered in 30% of the patients in response to decrease in serum phosphate levels. Phosphate levels usually returned towards 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 (≥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 (≥15% decrease of serum calcium from baseline) were also included, the response rates were 97% for the Aredia group and 66% 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)		
	Aredia	Didronel	p Value[1]
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

[1] Comparison between treatment groups

In both 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.

Twenty-five patients who had recurrent or refractory hypercalcemia of malignancy were given a second course of 60 mg of Aredia. Of these, 40% showed a complete response and 20% 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 treatment.

INDICATIONS AND USAGE

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.

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 administration of Aredia. A 3-month study in rats found cortical tubular changes including epithelial degeneration with intravenous doses ≥ 5 mg/kg, given once every two weeks. Following a recovery period (1 month), the degenerative changes were completely reversed. Focal fibrosis of renal tubules was partially reversed.

In two studies conducted in dogs, Aredia was given as a bolus intravenous injection either daily for 1 month or once a week for

3 months. In the 1-month study, tubulointerstitial nephritis, tubular degeneration and dilation occurred at 2 mg/kg. At recovery (1 month) the severity of these lesions was minimal or trace. Similar lesions (slight to marked severity) were noted in the 3-month study at 3 mg/kg and higher. However, no improvement of the lesions was observed following the 1-month recovery period.

Patients with hypercalcemia 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 enamel formation with single-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 (16%), hypokalemia (9%), hypomagnesemia (12%), and hypocalcemia (8-12%), 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.

Aredia has not been tested in patients who have class Dc renal impairment (creatinine >5.0 mg/dL). Clinical judgement should determine whether the potential benefit outweighs the potential risk in such patients.

Laboratory Tests

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

Drug Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Aredia was nonmutagenic in four mutagenicity assays: Ames test, nucleus-anomaly test, sister-chromatid-exchange study, and point-mutation test.

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

Pregnancy Category C

Aredia has been shown to increase the length of gestation and parturition in rats resulting in an increase in pup mortality when given orally at daily doses of 60 and 150 mg/kg/day from before pregnancy until after parturition. When corrected for oral bioavailability, each daily dose is approximately 0.7 to 1.7 times the highest recommended human dose for a single intravenous infusion. Oral doses of 25 to 150 mg/kg/day during the period of gestation failed to demonstrate any teratogenic, fetotoxic, or embryotoxic effects in rats or rabbits. Animal reproduction studies have not been conducted with intravenously administered Aredia. It is not known if intravenous Aredia can cause fetal harm when administered to pregnant woman or if it can affect reproduction capacity. There are no adequate and well-controlled studies in pregnant women. Aredia should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

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

Pediatric Use
Safety and effectiveness of Aredia in children have not been established.

ADVERSE REACTIONS
Transient mild elevation of temperature by at least 1°C was noted 24-48 hours after administration of Aredia in 27% of the patients in clinical trials.

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.

~~Uveitis was reported in 1 patient who had hypercalcemia of malignancy; another patient who had Paget's disease of bone developed mild iritis that was responsive to indomethacin and topical steroid. Both of these patients received Aredia in uncontrolled studies.~~

Four of 82 patients (4.9%) who received Aredia during the 2 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.

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 related to treatment with biphosphonates during comparative, controlled U.S. trials.

Biphosphonate-Related Adverse Experiences in Two U.S. Controlled Clinical Trials

	Percent of Patients		
	Aredia (N = 87)		Didronel (N = 35)
	60 mg	90 mg	7.5 mg/kg x 3 days
General			
Fatigue	0	12	0
Fever	20	18	9
Fluid overload	0	0	6
Infusion-site reaction	6	18	0
Moniliasis	0	6	0
Gastrointestinal			
Abdominal pain	2	0	0
Anorexia	2	12	0
Constipation	0	6	3
Gastrointestinal hemorrhage	0	6	0
Nausea	0	18	6
Ulcerative stomatitis	0	0	3
Respiratory System			
Dyspnea	0	0	3
Rales	0	6	0
Rhinitis	0	6	0
Upper respiratory infection	2	0	0
CNS			
Convulsions	0	0	3
Insomnia	2	0	0
Somnolence	2	6	0
Taste perversion	0	0	3
Abnormal vision	2	0	0

Cardiovascular			
Atrial fibrillation	0	6	0
Hypertension	0	6	0
Syncope	0	6	0
Tachycardia	0	6	0
Endocrine System			
Hypothyroidism	0	6	0
Hemic and Lymphatic System			
Anemia	0	6	0
Laboratory Abnormality			
Hypocalcemia	2	12	0
Hypokalemia	4	18	0
Hypomagnesemia	8	12	3
Hypophosphatemia	14	18	3
Abnormal hepatic function	0	0	3

OVERDOSAGE

One obese woman (95 kg) who was treated with 238 mg of Aredia/day for 3 days, experienced high fever (39.5°C), hypotension (from 170/90 mm-Hg to 90/60 mm-Hg), and transient taste perversion, noted about 8 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

Consideration should be given to the severity of as well as the symptoms of hypercalcemia. The recommended dose of Aredia in moderate hypercalcemia (corrected serum calcium of approximately 12-13.5 mg/dL) is 60-90 mg, and in severe hypercalcemia (corrected serum calcium, >13.5 mg/dL), is 90 mg, given as 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).

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.

A limited number of patients have received more than one treatment with Aredia for hypercalcemia. Retreatment with Aredia may be considered if hypercalcemia recurs. 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.

Preparation of Solution

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. The pH of the reconstituted solution is 8.0 - 7.4. The drug should be completely dissolved before the solution is withdrawn. The daily dose must be administered as an intravenous infusion over 24 hours. 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. Aredia must not be mixed with calcium-containing infusion solutions, such as Ringer's solution.

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

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

HOW SUPPLIED

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

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

Do not store above 86°F (30°C).

Caution: Federal law prohibits dispensing without prescription.

[illegible] Printed in U.S.A. [illegible]

C92-57 (Rev. 1/93)

CIBA

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