10/31/91

Aredia™ C91-47

Revision of C91-29 in accordance with FDA telefax of October 30, 1991.

Base Copy: C91-29

Aredia™

pamidronate disodium for injection
For intravenous infusion
~~ARD~~
Prescribing Information

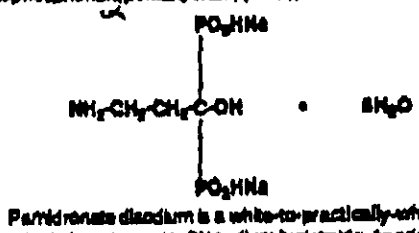
C91-47

phosphonic acid,

bis-, disodium salt,

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 monosodium (3-amino-1-hydroxypropylidene) bisphosphonate 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 ~~and skeletal metastases~~ 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 90 mg of Aredia over 4 or 24 hours, a mean of 61% (32-80%) of the drug was extracted in the urine within 72 hours. Body retention during this period was calculated to be a mean of 49% (20-69%) of the dose, or 29.3 mg (12-41 mg). The urinary-excretion-rate profile after administration of 90 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.

unchanged

range

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 50% 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 20% 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 lymphoma. 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, 82 patients who had hypercalcemia of malignancy were enrolled to receive 20 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 20 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 5-7 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 20 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, 86 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 28 to receive Didronel.

The mean baseline corrected serum calcium for the Aredia 60 mg and Didronel groups were 14.8 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 (≥ 10% decrease of serum calcium from baseline) were also included, the response rates were 97% for the Aredia group and 63% 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 11.8 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 8 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	14.8	13.8	
24	-0.5	-0.8	
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 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 known hypersensitivity to Aredia or other bisphosphonates.

WARNINGS

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

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.

moderate or severe

clinically significant

A 3-month study in rats found cortical tubular changes including epithelial degeneration with intravenous doses ≥ 6 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.

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 (8%), hypomagnesemia (12%), and hypocalcemia (8-12%), were reported in Aredia-treated patients. One case of hypocalcemia with symptomatic tetany has been reported during oral Aredia treatment. If hypocalcemia occurs, short-term calcium therapy may be necessary.

~~Although no relationship has been established, there have been rare reports of seizures in hypocalcemic patients who have been treated with bisphosphonates.~~

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

~~Local soft tissue symptoms (redness, swelling of indurations and pain on palpation) at the site of catheter insertion were most common (11%) in patients treated with 90 mg of Aredia. Symptoms with treatment resulted in rapid resolution in all patients.~~

creatinine. → and

Laboratory Tests

Serum calcium, electrolytes, phosphate, magnesium, 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. ~~No other drug interactions have been reported.~~

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 ($p < 0.0001$). 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 group. Aredia has not been administered intravenously in such a study.

dose →

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.

Drug-related local soft-tissue symptoms (redness, swelling or induration and pain on palpitation) 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.

was

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 pre-existing 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.

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.

Uveitis has been 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.

IF At least 18% 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. Comparative Clinical Trials
Percent of Patients

	Aredia (N = 67)		Didronel (N = 38)
	60 mg	90 mg	7.5 mg/kg x 3 days
General			
Fatigue	0	12	0
Fever	33	18	8
Fluid overload	0	0	8
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	8
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	18	0
Hypokalemia	4	18	0
Hypomagnesemia	8	12	8
Hypophosphatemia	14	18	3
Abnormal hepatic function	0	0	3

OVERDOSAGE

One obese woman (95 kg) who was treated with 286 mg of Aredia/day for 3 days, experienced high fever (39.8°C), hypotension (from 170/100 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. 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. The 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.
Cartons of 4 vials ..... NDC 0083-2001-04

Do not store above 86°F (30°C).

Caution: Federal law prohibits dispensing without prescription.

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CIBA

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