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ATTACH AL CONTRACTOR

Ciba-Geigy Corporation Attention: John R. Hanagan, M.D. 556 McTris 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

Solomon Sobel, M.D.

Director

Division of Metabolism and Endocrine Drug Products (HFD-510)

Center for Drug Evaluation and Research

5/4/93

1.7 # 101

C92-48 (Flev. 1092)

pamidronate disodium for injection For intravenous infusion

Prescribing information

DESCRIPTION

Aredia, parnidronate 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 startle, 'yophilized parnidronate disodium and 470 mg, 400 mg, and 375 mg of mannitotionate disodium and 470 mg, 400 parnidronate 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. Parnidronate disodium is designated chemically as phosphonic acid (3-arrino-1-hydroxypropylidene) bis-disodium. sait, pentahydrate, (APD), and its structural formula is:
POJHNa

NH, CH, CH, COH

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,H,NO,P,Na,-5H,O and its molecular weight is 369.1. Inactive ingredients. Mannitol, USP, and phosphoric acid (for

adjustment to pH 6.5 prior to lyophilization).

The principal pharmacologic action of Aredia is inhibition of bone recorption. Although the mechanism of antirecorptive action is not completely understood, several factors are thought to contribute to

this action. Aredia adsorbs to calcium phosphate (hydroxypasitie) crystals in borne and mary directly block dissolution of this mineral component of bone. In vitro studies, 350 suggest that inhibition of octeoclast activity contributes to inhibition of borne recorption. In animal studies, at doses recommended for the treatment of hyper-calcernia. Aredia inhibits bone resorption apparently without inhibiting bone formation and immeralization. Of relevance to the treatment of hyper-calcernia of mailignancy is the finding that Aredia inhibits the accelerated bone resorption apparently without inhibiting bone formation and immeralization. Of relevance to the treatment of hyper-calcernia of mailignancy is the finding that Aredia inhibits the accelerated by various turnors in animal studies.

In cancer patients who had minimal or no bony involvement who were given an intravenous infusion of 80 mg of Aredia over 4 or 24 hours, a mean of 51% (32-80%) of the drug was excreted unchanged in the unine 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 urhary-excretion-rate profile after administration characteristics with an alpha nati-file of 1.6 hours and a bera half-file of 27.2 hours. There are no human pharmacolchectic 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 radiclabeled Aredia in rats, approximately 50-80% of the compound was rapidly adsorbed by bone and slowly eliminated from the body by the lidneys. In rats given the indreys over 24-45 hours. Studies in rats injected with radio-labeled Aredia showed that the compound was rapidly cleaned from the body by the lidneys over 24-45 hours. Studies in rats injected with radio-labeled Aredia and unimality by bones, liver, spiesn, teeth, and tractival carrillate.

and tracheal cardiage. Radioactivity was eliminated from most soft tissues within 1-4 days; was detectable in liver and spieen for 1 and 3 months, respectively; and remained high in bones, traches, and 3 months, respectively; and remained high in bones, traches, and teeth for 6 months after dosing. Sone uptake occurred preferentially in areas of high bone tumover. The terminal phase of plimination half-life in bone was estimated to be approximately 300

Serum phosphate levels have been noted to decrease after administration of Aredia, presumably because of decreased release

roid hormone levels, which are usually suppressed in hypercalcemia associated with malignaricy, 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/creathline and urinary hydroxyprolihe/creat-infine r los oecreose 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 will an antirescriptive pharmacologic action.

Hypercalcerris of staffgrancy

Octeoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in metastatic bone disease and hypercalcerris of malignancy. Excessive resease of calcium into the blood as bone is resorbed results in polyunia and gastrointestinal disturbances, with progressive dehydration and decressing 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 hypercalce-

in patients who have breast cancer; squamous-cell turnors of the lung or head and neck; renal-cell carcinome; and certain hematinogic malignancies, such as multiple myeloms and some types or hymphomes. A few less-common malignancies, including vascactive intestinal-peptide-producing turnors and cholangiocarcinoms, 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 mechanic involved. mechanism involved. Most cases of hypercalcemia associated with malignancy occur

in humoral hypercalcernia, octooclasts 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 hypercalcernia usually occurs in squamous-cell malignancies of the lung or head and neck or in gentlourinary tumors such as renal-cell carcinoms or ovarian cancer. Skeletal metastases may be absent or minimal in these

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

Total serum calcium levels in patients who have hypercalcemia, of malignancy may not reflect the severity of hypercalcemia, since concomitant hypositiuminemia 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 oftenused in place of measurement of lonized calcium; several nomograms are in use for this type of calculation (see LOSAGE AND ADMINISTRATION).

Clinical Trials in one double-blind clinical trial, 52 patients who had hypercaling one double-blind clinical trial, 52 patients who had hypercaling of malignancy were enrolled to receive 30 mg, 60 mg, or 90 mg of Aredia as a single 24-hour intravenous influsion if their corrected serum calcium levels were >12.0 mg/dL after 48 hours

(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. 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 treatment. initiation of trustment 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 ng, 60 mg, and 90 mg of Aredia, respectively, had normal corrected serum calcium levels. Many patients

In a second double-blind, controlled clinical trial, 65 cancer

patients who had corrected serum calcium levels (-212.0 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 of 7.5 mg/kg of Didronel (eftdronate 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 /iredia 80 mg and Didronel groups were 14.6 mg/dL and 13.8 mg/dL.

By day 7, 70% of the patients in the Aredia group and 41% of outlents in the Didronel group had normal corrected serum Jeicium levels (P <0.05). When parulal responders (≥15% decrease of serum calcium from baselin-) were also included, the response rates were 97% for the Aredis group and 65% for 1:3 Didronel group (P <0.01). Mean corrected serum calcium for the Aredis and Didronel groups decreased from bureline values to 10.4 and 11.2 mg/dl., respectively, on day 7 and day 14, 43% of patients in the Aredia group and 10% of satients in the Didronel group stiff had normal corrected serum cultural 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 effection corrected serum calcium is summarized in the following table.

Change in Corrected Serum Calcium by Time

	from Initia	itiation of Treatment	
Time	Mean Change	from Baseline in Co	rected Serum
3	•	Calciu (mg/dL)	:
	Aredia	Didionel	p Value
Baseine	14.6	13.8	
24	ė ė		
\$	-1.5	÷	
አ	-2.6	-2.0	
8	3.5	-2.0	60.01
8	<u>+</u>	-2.5	<0.01
Comparison	mparison between treat	sen 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 hypercalcents of malignancy were given a second course of 80 mg of Aredia. Of these, 40% showed a complete response and 20% showed a partial response to the retreatment, and these respondents had about a 3 mg/dL fall in mean corrected serum calcium levels 7 days after treatment.

INDICATIONS AND USAGE

cernia 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 compaction of hypercalcemia, 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. treatment of moderate or severe hyperculcemia associated with malignancy, with or without bone metastases. Patients who have either epidermoid or non-epidermoid tumors respond to treatment with Avedia. Vigorous saline hydration, an Integral part of hypercal-A: adia, in conjunction with adequate hydration, is indicated for the

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

WARNINGS

intravenous, boks administration of Anedia. A 3-month study in rats found contical tubular changes including aphthelial degeneration with intravenous doses > 5 mg/lg, given once every two weeks. Following a recovery period (1 month), the degenerative changes were completely reversed. Focal fibrosis of renal tubules In both rats and dogs, nephropathy has been associated with

was partially reversed.

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

Aredia® pamidronate disodium for injection

month) the severity of these lesions was minimal or trace. Similar lesions (slight to maried severity) were noted in the 3-monthatudy 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 intravecous intusion 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 ename; formation with single-dose administration of bisphosphonates. The clinical significance of these findings is

unknown. PRECAUTIONS

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 asymptometic hypophosphatemia (16%), hypophosphatemia (16%), 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, shortterm 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 outweights the potential risk in such patients.

aboratory Tests

Serum calcium, electrolytes, phosphate, magnesium and creati-nine, and CBC, differential, and hematocrithemoglobin must be closely monitored in patients treated with Aradia. Patients who have preexisting anemia, leukspenia, 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.
Carcinogeneeta, Mutageneeta, Impairment of Fertility
Carcinogeneeta, Mutageneeta, 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.40.00001). Although this
condition was also observed in fermales, the incider.co was not
statistically significant. When the dose calculations were adjusted
to account for the limited oral bloavailability 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: Arnes
test, nucleus-anormaly test, sister-chromatid-exchange study, and

point-mutation test.

in rats, decreased fartifity 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 intraverously

Pregnancy Category C Aradia has been shown to increase the length of gestation and Aradia 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 80 and 150 mg/lg/day from before pregnancy untit after parturition. When corrected for oral bio pregnancy untit after parturition. When corrected for oral bio availability, each daily dose to approximately 0.7 to 1.7 times the highest recommended human dose for a single intravenous infusion. Oral doses of 25 to 150 mg/lg/day during the period of gestation falled to demonstrate any teratogenic, fedoloxic, or embryoloxic effects in rats or rabbia. Animal reproduction studies have not been conducted with intravenously administered Aredia. It is not known if it 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.

the potential benefit justifies the potential risk to the listus.

Nursing Mothers

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

Pediatric ties

alety and effectiveness of Aradia in children have not been stablished.

ADVERSE REACTIONS
Transient mild elevation of wroperature 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 palpattion) at the site of catheter intention were most common (18%) in patients treated with 80 mg of Aredia.

When all on-therapy events are considered, that rate rises to 41%. Symptometic treatment resided in rapid resolution in all patients. Uveits was reported in 1 patient who had hypercalcemia of matignancy; another patient who had Pager's disease of bone developed mild liftis that was responsive to indomethation and optical steroid. Both of these patients received Aredia in uncontrolled studies.

Four of 82 patients (4.9%) who received Aredia during the 2 I.S. controlled hypercalcental cirilical studies were reported to ht.:... ad 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 a and the occurrence of seizures cannot be ruled out.

At least 15% of patients treated with Aredia for hypercalcentia of malignancy also experienced the following adverse events during a clinical trial:

General: Fluid overload, generalized pain
Cardiovascular: Hyperferation
Cardiovascular: Abdominal pain, anorenia, constipation, nau-

sea, vomiting

Genitournary: Urinary tract infection

Ausculoskeietal: 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 bisphosphonales during comparative,

60.08 60.09	Aradia (N = 67)	Percent	in Two U.S. Controlled Clinical Tricks
7.5 mg/kg x 3 days	Didronel (N = 35)	Percent of Patients	Minical Triets

temic and Lymphatic	typothyroidem	Indocrine System	Syncope	typertension	Arial fibrillation	Serdiovascular	Shormal vision	faste perversion	Somncience	neomnia	Convulsions	*	nfection	Avois metal acou			yapnes	hepiratory System	Iconative stomatitis		hemorrhage	astrointestinal	onstipation	norexia	bdominal pain	netrointestinal	oniliasis 0	fusion-site reaction	uid overload	Ver 2		
	0	•	00	, 0	0		N	0	2	~	0	ı	N		O	0	0		0	0	0		0									•
a T	6.	•	a	. 65	.		0	0	o o	O	0	1	0		6	Φ	0		0	₩	9		σ.	ಸ	0		on.	ਛ	0	5	ฆ	4
0	0)	00	o c	0		a		0	• •	. ω)	0		0	0	ω)i	ယ	Φ	0	•	u	0	a		0	0	O.	40	0	

Laboratory Abnormality Hypocalcenia Hypokalemia Hypomagnesemia Hypomagnesemia Hypophosphatemia Abnormal hepatic # a + N まだまだ **6000**

function

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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%) mmHg to 30/60 mmHg), and transient taste perversion, noted about 6 hours after the first infusion. The fever

and hypotension were rapidly corrected with storoids.

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

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. Albuministial, single-dose, juttavenous infusion over 24 hours. Albuministial, single-dose, intravenous infusion over 24 hours. Albuministial, single-dose, intravenous infusion over 24 hours. Albuministial, single-dose, intravenous infusion may be sufficient for treating mid, asymptomatic hypercalcemia. Overhydration should be avoided in patients who have potential for cardiac failure. In hypercalcemia secciated with hematologic malignancies, the use of glucocorticoid therapy may be helpful.

A limited number of patients have received more tran one treatment with Aredia may be considered if hypercalcemia. Retreatment with Aredia may be considered if hypercalcemia. The dose and manner of retreatment is identical to that of the initial therapy.

Preparetion of Solution
Aredia is reconstituted by adding 10 mL of Sterile Water for Aredia is reconstituted by adding 10 mL of Sterile Water for Injection, USP, to each visit resulting in a solution of 30 mg/10 mL, is 60 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 influsion 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. Avedia must not be mixed with catcham-containing infusion solutions, such as Ringer's solution.

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

And is reconstituted with Sterile Water for Injection may be stored under refigeration at 38-46°F (2-8°C) for up to 24 hours.

Follow SuppeluED

Viair-90 mg - each contains 90 mg of sterile, lyophilized parnidronate

disodium and 375 mg of mannitol, USP NDC 0083-2606-01

Caution: Federal law prohibits dispensing without prescription Do not store above 86°F (30°C)

C92-48 (Rev. 10/92)

Printed in U.S.A.

CIB

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

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ORIGINAL

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

-001 SOF-001 (BL) **Eatielings** SCS-002 (BL)

Aredia ● pamidronate disodium for injection

WDA No: 30-036 Ro'd. 2-8-9:
Reviewed by:

60 mg/vial Label, Code # 893140

NDC 8083-2806-01 FSC 8126

Aradia®
peraldronate disodium
for injuction
For intravenous infusion
Sterile, Lyophikized

60mg/vial

Do not mix with calciumcontaining infusion solutions.

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

CIBA

LOT

893140

Aredia • pamidronate disodium for injection

60 mg/vial Carton, Code # 875100

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UOI\$TUUI For Intravenous lor injection mulbosio stanorbimaq

Aredia © 60 mg/vial

NDC 0083-5009-04 LBC 8159

875100

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. 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 tull directions see package insert.
See side panel for lot number and expiration date NDC 0083-2606-01 FSC 8126

Aredia® 60 mg/vial pamidronate disodium

for Injection For Intravenous infusion

Sterile, Lyophilized



Mfd. by: Clos-Geigy Ltd. Basie, Switzerland

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





Final Printed Labeling for Supplement S-002

NDA 20-036

Labeling: SCS-002/BL)

Aredia • NDA No: 20-036

Pamidronate disodium for injection Reviewed by:

ORIGINAL

NDC 0083-2606-01 FSC 81%

90 mg/vial Label, Code # 893130

Aredia®
pemigronate disadium
for Injection
For Intravenous Infusion
Sterile, Lyophilized

90_{mg/vlal}

Do not mix with calciumcontaining infusion solutions. Mfd. by: Ciba-Geigy Ltd. Baste, Switzerland Dist. by: Ciba Pharmaceutical Co. Div. of Ciba-Geigy Corp. Summit, NJ 07901

CIBA

EXP

893130

Aredia •
pamidronate disodium for injection
90 mg/vial Carton, Code # 679650

IBIV F

Aredia[®] 90 mg/ visit pamile of solutions to the ction to the ction of the ction o

E2C 8138

with the same of t

NDC 0083-5008-04

Aredia is reconstituted by adding 10 mL of Sterile Water for Injection, USP, to each viat, resulting in a solution of 90 mg/10 mL. The drug should be completely dissolved before the solution is withdrawn. The daily doce 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.

679650

NDC 0063-2609-01

FSC 8136

Aredia® 90 mg/vial

pamidronate disodium for injection

For intravenous Infusion Sterile, Lyophilized





Mid. by: Ciba-Geigy Ltd. Basie, Switzerland

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



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ORIGINAL

AUG 3 1892

CHEMIST'S REVIEW

1. ORGANIZATION	NDA NUMBER
DMELP	20-036
	24 000
3. NAME AND ADDRESS OF APPLICANT	4. SUPPLEMENT
The same and the s	NUMBER, DATE
Ciba Coima Dhammacashical Division	S-002, 3-26-92
Ciba-Geigy Pharmaceutical Division	
556 Morris Avenue	
Summit, N.J. 07901	
5. NAME OF DRUG 6. NONPROPRIETARY	
	lium 7.AMENDMENT #.DATE
for injection	
8. SUPPLEMENT PROVIDES FOR:	a new dosage strength:
90 mg lyophilized vial	•
9. PHARMACOLOGICAL CATEGORY 10. HOW I	MSPERSED
Bone reabsorption inhibitor RX	11. RELATED
Edic Legeor Foron Hilloroof IV	DOCUMENTS
	s-001. 12-27-91
4.0 Publica (CE) mustica (A.O. Publica)	
12. DOSAGE FORM 13. POTENCY	
injection 30mg, 60 mg,	90 mg
14. CHEMICAL NAME AND STRUCTURE	
phosphonic acid (3-amino	-1-hvoxypropyliene)
bis-, disodium salt, pentahydrate of oNq	
\ - P	.o. 5 H20
O SHL H	
H Chr	
1.5 COMMENTO	•*
15. COMMENTS	
-	
	-
16 CONCLUSIONS AND RECOMMENDATIONS	
The supplement is approvable: issue lett	er requesting labels
and package insert reflecting the new dose	
and package insert refrecting the new dose	ige strength.
17 DEUTEUE	
17. REVIEWER	
- NAME SIGNATURE	DATE COMPLETED
Kathleen Hillman Kat le Wal-	8-3-92
DISTRIBUTION: ORIGINAL JACKET	REVIEWER
DIVISION FILE ,	
R/D initialed by a/Chill	
M. lan	
01'1	

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

Solomon Sobel, M.D.

Director

Division of Metabolism and

Endocrine Drug Products (HFD-510)

Center for Drug Evaluation and Research

6/8/13

ORIGINAL APR - 2 1993

20-036 (S-005) Pamidronate disodium Inj. (Aredia) Ciba-Geigy

Review completed: 3/31/93

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.

CC: NDA 20-036 (S-005)

HFD-340 HFD-510

HFD-510/SND/Pierce/4/2/93

Aredia® C92-57 (Rev. 1/93)

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

Base cooy: C92-45

C92-57 (Rev. 1/93)

APPROVED 6.9.9

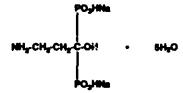
Aredia*

pamidronate disodium for injection For Intravenous Infusion

Prescribing Information

DESCRIPTION

DESCRIPTION Aredia, perhitronate disodium, (APD), is a bone-resorption inhibitor available in vials for intravenous administration. Each violationaline 30 mg of sterile, lyophilized perhitronate disodium and 470 mg of memitot, USP. The pH of a 1% solution of perhitronate 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. Parridronate disodium is designated chemically as phosphonic acid (3-armino-1-hydroxypm-pylidene) bit-, disodium salt, pentahydrate, (APD), and its structural formula is: tural formula la:



Parnidronate disodium is a white-to-practically-white powder. It is soluble in water and in 2N sodium hydroride, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is C.J.,NO,P.Ne,-Si-I,O and its molecular wright is 369.1.

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

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY

The principal pharmacologic action of Aradia is inhibition of bone recorption. Although the mechanism of antirecorptive action is not completely understood, several factors are thought to contribute to this action. Aradia adsorbs to calcium phosphate (hydroxyspatile) 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 recorption. In advance recommended for the treatment of hydroxyspatial studies at disease recommended for the treatment of hydroxyspatials. ossecting activity controlles to inholition of bore-reorption. In-inimal studies, at doses recommended for the treatment of hyper-calcomia, Anedia inhibits bone resorption apparently without inhib-ling bone formation and mineralization. Of relevance to the treatment of hypercalcomia of malignancy is the finding that Aredia, inhibits the accelerated bone recorption that results from ossectast

inhibits the accelerated bone recorption that results from outsociast inhibits the accelerated bone recorption that results from outsociast inprescrivity induced by various tumors in animal studies.

In cancer patients, who had minimal or no bony involvement who were given an intravenous infusion of 80 mg of Aredia over 4 or 24 hours, a mean of 51% (32-90%) 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 20-88%) 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 biphaels disposition characteristics with an alpha half-life of 1.6 hours and a beta half-life of 27.2 hours. There are no human pharmacokinetis 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 rate, approximately 50-60% of the compound was rapidly adsorbed by bone and slowly eliminated from the body by the lidencys, in rate given 10 mg/ng 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 rate injected with radio-

administration and was then redistributed to bone or eliminated by the kidneys over 24-48 hours. Studies in rais injected with radio-labeled Aredia-howed that the compound was rapidly cleared from the circulation and taks, in up mainly by bones, liver, splean, teeth, and trached cartilage. Radioactivity was eliminated from most soft tissues within 1-4 days; was detectable in liver and splean for 1 and 3 months, respectively; and remained high in bones, traches, and teeth for 6 months after doeing. 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 ad-ministration of Aredia, presumably because of decreased release of phosphate from bone and increased renal accretion as parathy-

rold hormone levels, which are usually suppressed in hypercalcemia associated with marignancy, return towards normal. Phosrate therapy was administered in 30% of the patients in response decrease in serum phosphate evels, Phosphate levels usually urned towards normal within 7-10 clays.

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 antirescriptive pharmacologic action. Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone recorption 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 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 bond-resorption and adequate fluid administration to correct volume deficits are therefore essential to the management of hypercalcemia.

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

In humoral hypercalcemia, osteoclasts are activated and bone recorption is stimulated by factors such as parathyroid-hormône-related protein, which are elaborated by the turnor and circulate systemically. Humoral hypercalcemia usually occurs in sque-mous-cell malignancies of the lung or head and neck or in genlicurinary turnors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by turnor cells can also result in hypercalcernia due to local turnor products that stimulate bone recorption by osseciasts. Turnors commonly associated with locally mediated hypercalcernia include breast cancer and multiple myelonis.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the seventy of hypercalcemia, since incomitant hyposibuminemia is commonly present. Ideally, ioned 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 pinos of measurement of ionized calcium; several nomograms a.e 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/dt. after 48 hours of saline hydration.

The mean baseline corrected serum calcium for the 30 mg, 80 mg, and 90 mg groups were 13.8 mg/dL, 13.8 mg/dL and 13.3 mg/d., respectively.

The majority of patients (64%) had decreases in albumincorrected serum calcium levels by 24 hours after initiation of treatment. Mean-corrected serum calcium levels at days 2-7 after initiation of treatment with Aradia were significantly reduced from baseline in all three dosage groups. As a result, by 7 days after initiation of treatment with Aradia, 40%, 61%, and 100% of the patients receiving 30 mg, 60 mg, and 90 mg of Aradia, respectively, had normal corrected serum calcium levels. Many patients (33-63%) 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, 85 cancer

patients who had corrected serum calcium levels of ≥12.0 mg/di, after at least 24 hours of saline hydration were randomized to receive either 80 mg of Aredia as a single 24-hour intravenous introl or 7.5 mg/tg of Didionel (stidronase disodium) as a 2-hour intravenous infusion daily for 3 days. Thirty patients were randomized to receive Aredia and 35 to receive Didronal.

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 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 straiter (7 and 5 days, respectively). The time course of effect on corrected serum calcium is summarized in the following table.

Change in Corrected Serven Catches by Time from Initiation of Treatment

Time (hr)	Mean Change from Baseline in Corrected Serum Calcium (mg/dL)							
 ,	Aredia	Didronel	p Value					
Baseline	14.0	13.8						
24	-0.3	-0.5						
48	-1.5	-1.1						
72	-2.6	-2.0						
96	-3.5	-2.0	<0.01					
168	-4.1	-2.5	<0.01					

* Comparison between treatment groups

In 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 80 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

Anedia, 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 turnors 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 ditrettos). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac tailure, 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 hyperparathyroidiem or with other non-turnor-related conditions has not been established.

CONTRAINDICATIONS

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

WARNING

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 boluintravenous injection either daily for 1 month or once a week for

3 months. In the 1-month study, tubulointers (itial 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 lesione 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

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Standard hypercalcomia-related metabolic parameters, such as serum levels of calcium, phosphete, magnetum, and potaselum should be carefully monitored following initiation of therapy with Aredia. Cases of asymptomatic hypophosphatemia (18%), hypotalcimia (19%), hypomagnesemia (12%), and hypocalcamia (8-12%), were reported in Aredia-treated patients. Rere cases of symptomatic hypochicemia (including tetany) have been reported in association with Aredia therapy. If hypochicemia occurs, short-

term calcium therapy may be recessary.

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

Laboratory Toots

Serum calcium, electrolytes, phosphere, magnesium and creati-nine, and CBC, differential, and hematocrit/hemoglobin must be closely monitored in patients treated with Aredia." Patients who nave preexisting enemia, isukopenia, or thrombocytopenia should be monitored carefully in the first 2 weeks following treatment.

Drug Interact

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

Carcinogenesia, Mutagenesia, Impairment of Fortility in a 104-week carcinogenicity study (daily oral administration) in rate, there was a positive dose response relationship for benign advensi phe-chromocytoms in males (p <0.00001). Although this condition was also observed in females, the incidence was not sizatistically significant. When the dose calculations were adjusted to account for the limited oral blosvallability of Aredia in rate, the lowest daily dose associated with advent pheochromocytoms 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: Arnes test, nucleus-anomaly test, alster-chromatid-exchange study, and point-mutation test.

In rats, ducreased 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.

Prognancy Category C

Aredia has been shown to increase the length of gestation and parturition in rate resulting in an increase in pup mortality when given orally at daily doses of 60 and 150 mg/tg/day from before pregnancy until after parturition. When corrected for oral bloavallability, 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/tg/day during the period of gestation failed to demonstrate any teratogenic, letotoxic, or embryotoxic effects in rate 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 pregnent 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 exerclead when Aredia is administered to a nursing woman.

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Pediatric Use

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rechallenge.

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

Drug-related local soft-tiesue symptoms (redness, swelling or induration and pain on palpation) at the site of catheter insertion were most common (18%) in parients 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.

- Uverlie: vere-reported in 1-patient who had hyperealcomin of < malignary; enother patient who had Pageto-disease of bone developed mild little that may responsive to indometherin and respinal staroid. Sath of these patients retaived Aradia in uncon-

Four of 82 futterts (4.9%) who received Arudia, uring the 2 U.S. controlled hypercalcernia clinical studies were reported to have had setzures, 2 of whom had prestiting 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 setzures cannot be ruled out.

At least 15% of patients treated with Aredia for hyperculcemia of malignancy also experienced the following adverse events during a clinical trial:

Centeral: Fluid overtead, generalized pain

Centeral: Substantians

Cardiovascular: Hypertension
Gastroinsesthal: Abdorninal pain, anorests, constitution, neu-

sea, vornting Genitourinary: Urinary tract infection Musculashelatal: Bone pain

Laboratory abnormality: Anemia, hypokalemia, hypomagne-

semia, hypophosphaterria.

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 treasment with bisphosphonates during compensative. controlled U.S. trials.

Biophosphonets-Related Adverse Experiences in Tire U.S. Controlled Clinical Tricle

Percent of Patients

	Aradia_	(N = 47)	Dictronal (N. s. 36)
	80 m g	20.mg	7.5 mg/kg x 3 dans
General			
Fatigue	0	12	0
Fever	20	16	9
Fiuld overload	0	0	6
Infusion-site	_		
reaction)	6	18	0
Monitiesis	0	6	0
Controlntertinal			
Abdominal pain	2	0	0
Anoresia	2	12	0
Constigution	0	6	3
Gastrointestinal			
hemorrhage	0	8	0
Naveni	0	18	6
Ulcerative	_		
atomatikis .	0	0	3
Respiratory System	•		
Dyspres	0	0	3
Rales	G	6	0
Rhinitis	0	6	0
Upper respiratory			
infection	5	0	0
CNS			
Convulsions	0	0	3
ineomnia	ž	ŏ	ŏ
Somnoience	Š	ě	Ö
Tattle parversion	ŏ	ŏ	3
Abnormal vision	ž	Ŏ	Ō

Cardiovescular			
Atrial fibridation	Ð	6	0
Hypertension	0	6	0
Syncope	Ď	6	0
Tachycardia	ŏ	6	ŏ
Endecrine System			
Hypothyroidlern	0	6	0
Hemic and Lympholi	c System	1	
Anomia	Ō	6	0
Laboratory Abnormal	lty		
Hypocalcemia	2	12	· 0
Hypokalemia	4	18	0
Hypomagnesemia		12	3
Hypophosphatemia	14	16	3
Abnormal hapatic	. ,		
hardion	a	C	3

OVERDOSAGE

One obese women (96 kg) who was trusted with 295 mg of Anedlavday for 3 days, experienced hips fever (38.5°C), hypotension (from 170/90 mmHg to 90/90 mmHg), and transient taste powersion, noted about 6 hours after the first infusion. The lever

and hypoteneion were rapidly corrected with steroids.

If overdougge occurs, symptomatic hypocalcemia could also
result; such patients should be treated with show 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 wyrrpunna or rypercaneres. The reconstructed does or Areos. In moderate hypercalcental (corrected serum calcium of approximately 12-13.5 mg/dL) is 60-90 mg, and in severe hypercalcenta (corrected serum calcium, > 13.5 mg/dL), is 90 mg, given as an initial, single-does, infravenous infusion over 24 hours. Albumin-corrected serum calcium (CCa, mg/dL) = serum calcium, mg/dL + 0.8 (A.D. serum abumés add). 0.8 (4.0 - serum albumin, g/RL).
Vigorous saline hydration alone may be sufficient for treating

mild, asymptometic hypercalcumia. Overhydration should be avoided in patients who have potential for cardiac failure, in hypercalcernia associated with hematologic malignancies, the use of plucoconticold therapy may be helpful.

A limited number of patients have received more than one

treatment with Aradia for hypercalcernia. Retreatment with Aradia. may be considered if hypercalcemia recurs. It is recommended that a minimum of 7 days stapes 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 visit, resulting in a solution of 30 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 invavenous infusion over 24 hours. The recommended dose should be diluted in 1000 mL of sterile 0.48% or 0.9% Sodium Chloride, USP, or 5% Destrose injection, USP. This infusion solution is stable for up to 24 hours at reportant, costs. I the expension section is seated for up to go notife it is not temperature. Aredia must not be mixed with calcium-containing infusion solutions, such as Finger's solution.

Motor Parenterel drug products chould be inspected visually for particulate another and dispotention prior to ediminiotration, whenever coluber and container permit.

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

HOW SUPPLIED

Do not store above 66"F (30"C). Causion: Federal law prohibits dispensing without prescription.

C92-57 (Rev. 1/93)

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

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