500
200
100-S
NDA 30036
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,

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

5/4/93
Final Printed Labeling for Supplement S-001
NDA 20-036

Aredia®
 pamidronate disodium for injection

60 mg/vial Label, Code # 893140
Aredia®
pamidronate disodium for injection
For intravenous injection
 sterile, lyophilized
90 mg/vial

Do not mix with calcium-containing infusion solutions.
Made by
Ciba Geigy Corp.
Basel, Switzerland
Distributed by
Ciba Pharmaceutical Co.
400 Park Ave.
Summit, New Jersey 07901
EXP
LOT
893130
Final Printed Labeling for Supplement S-002
NDA 20-036

Aredia®
pamidronate disodium for injection
90 mg/vial Carton, Code # 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 The drug should be completely dissolved before the solution is withdrawn.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.

Mfd. by:
Ciba-Geigy Ltd.
Basle, Switzerland
Dist. by:
Ciba Pharmaceutical Co.
Div. of Ciba-Geigy Corp.
Summit, NJ 07901
1. ORGANIZATION
DMELP

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, 3-28-92

5. NAME OF DRUG
Aredia™

6. NONPROPRIETARY NAME
pamidronate disodium

7. AMENDMENT #, DATE
for injection

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
30 mg, 60 mg, 90 mg

14. CHEMICAL NAME AND STRUCTURE
phosphonic acid (3-amino-1-hydroxypropylene)
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
Kathleen Hillman

SIGNATURE

DATE COMPLETED
8-3-92

DISTRIBUTION: ORIGINAL JACKET REVIEWER

DIVISION FILE
R/D initiated by
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,

[Signature]

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

[Signature]
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
Aredia® C92-57 (Rev. 1/93)

Revision of current C92-45 in accordance with FDA letter of October 9, 1962: In ADVERSE REACTIONS section, replace third paragraph to include additional information regarding ocular side effects.

Circle copy: C92-45

Aredia® C92-57 (Rev. 1/93)

Areodia®

diolumetric dield for injection

For Intravenous Infusion

Prescribing Information

DESCRIPTION

Areodia, pamidronate disodium, (PDS), is a bone-resorption inhibitor available in vials for intravenous administration. Each vial contains 20 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 8.2. Areodia, a member of the group of chemical compounds known as bisphosphonates, is an analog of pyrophosphate. Pamidronate disodium is designated chemically as phosphoric acid (2-hydroxy-1-hydroxypropylidene) bis, disodium salt, pamidronate, (PDS), and its structural formula is:

\[ \text{Pamidronate disodium} = \text{PO}_4\text{H}_2\text{Na}_2\text{H}_2\text{O} \]

Pamidronate disodium is a white-to-pale yellowish-white powder. It is soluble in water and in 2N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid, and practically insoluble in organic solvents. Its molecular formula is \( \text{C}_2\text{H}_9\text{O}_6\text{P}_2\text{Na}_2\text{H}_2\text{O} \) and its molecular weight is 388.1.

CLINICAL PHARMACOLOGY

The principal pharmacologic action of Areodia is inhibition of bone resorption. Although the mechanism of antiresorptive action is not completely understood, several factors are thought to contribute to this action. Areodia arrests calcium phosphate (hydroxyapatite) crystals in bone and may directly or indirectly 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, all doses recommended for the treatment of hypercalcemia, Areodia inhibits bone resorption in sham-operated rats, rabbits, and dogs.

In cancer patients who had renal or no bony involvement who were given an intravenous infusion of 80 mg of Areodia over 4 or 8 hours, a mean of 81% (52-80%) of the drug was excreted unchanged in the urine within 72 hours. Early retention during this period was calculated to be a mean of 49% (range 30-69%) of the dose, or 39.3 mg (12.41 mg). The urinary-excretion-time profile after administration of 80 mg of Areodia over 4 hours exhibited biphasic disposition characteristics with a half-life of 1.8 hours and a beta half-life of 27.4 hours. There are no human pharmacokinetic data for Areodia on the 80 mg doses in patients who have either renal or hepatic insufficiency. The rate of elimination of Areodia from bone has not been determined.

After intravenous administration of radio-labeled Areodia in rats, approximately 50-60% of the compound was rapidly absorbed by bone and slowly eliminated from the body by the kidneys. In rats given 10 mg/kg bolus injections of radio-labeled Areodia, approximately 30% of the compound was found in the liver shortly after administration and was then redistributed to bone anteriorly by the kidneys over 24-48 hours. Studies in rats injected with radio-labeled Areodia showed that the compound was rapidly eliminated from the circulation and taken up mainly by bone, liver, spleen, teeth, and intestinal contents. Radioactivity was also eliminated from most soft tissues within 4-8 days, detectable in liver and spleen for 1 and 3 months, respectively; and retained high in bone, teeth, and soft tissue 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 Areodia, presumably because of increased release of phosphate from bone and increased renal excretion as parathy-
...and hormone levels, which are usually suppressed in hypercalcemia associated with malignancy, return towards normal. Phototherapy was administered in 30% of the patients in whom plasma calcium levels increased, but did not decrease in serum phosphate levels. Prophylactic therapy was usually given to those patients who were found to have hypercalcemia. Urinary calcium levels and urinary hydroxyproline/creatinine ratios decreased and usually returned to within the normal range after treatment with Areida. These changes occur within the first week after treatment. Patients who were given prophylactic therapy did not experience calcium-related side effects.

Hypercalcemia of Malignancy

Circulating hypercalcemia 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 increasing 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 and diuresis 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 polypeptide-producing tumors and cholangiocarcinoma, have a high incidence of hypercalcemia as a paraneoplastic complication. Patients who have hypercalcemia of malignancy can generally be divided into two groups, according to the pathophysiologic mechanisms 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 carcinoma of the lung or head and neck or in genitourinary tumors such as renal-cell carcinomas or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Excessive bone loss by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by receptors for parathyroid hormone.

Total serum calcium levels in patients who have hypercalcemia of malignancy are not reduced, and the history of normal bone turnover or normal hypercalcemia is uncommon. Ideally, total calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or readily available in many clinical situations. Therefore, adjustment of the total serum calcium level 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, 62 patients who had hypercalcemia of malignancy were enrolled to receive 30 mg, 60 mg, or 90 mg of Areida 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 (84%) had decreases in albumin-corrected serum calcium levels by 24 hours after initiation of treatment. Moreover, corrected serum calcium levels decreased by 7.0 mg/dl after initiation of treatment with Areida were significantly reduced from baseline in all three dosage groups. As a result, by 7 days after initiation of treatment with Areida, 60%, 61%, and 100% of the patients receiving 30 mg, 60 mg, and 90 mg of Areida, respectively, had normalized serum calcium levels. Many patients (53%-58%) in the 60 mg and 90 mg dosage groups continued to have normal-corrected serum calcium levels, or a partial response (5%-15% decrease of corrected serum calcium from baseline), at day 14.

In a second double-blind, controlled clinical trial, 63 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 Areida as a single 24-hour intravenous infusion of 7.5 mg/kg or DPN (dextrose 5% and sodium citrate) as a 2-hour intravenous infusion daily for 3 days. Thirty patients were randomized to receive Areida and 33 to receive DPN.

The mean baseline corrected serum calcium for the Areida 60 mg and DPN groups were 14.8 mg/dl and 13.8 mg/dl, respectively.

By day 7, 70% of the patients in the Areida group and 41% of the patients in the DPN group had normal corrected serum calcium levels (P < 0.05). Changes in corrected serum calcium from baseline were also included. The response rate was 97% for the Areida group and 66% for the DPN group (P < 0.01). Mean corrected serum calcium for the Areida and DPN 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 Areida group and 16% of patients in the DPN group still had normal corrected serum calcium levels, or maintenance of a partial response. For responders, the median duration of response was similar (7 and 9 days, respectively). The time course of effect on corrected serum calcium is summarized in the following tables.

### Change in Corrected Serum Calcium by Time and Dose of Treatment

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Mean Change from Baseline</th>
<th>Calcium (mg/dl)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.0</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>-1.8</td>
<td>10.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>48</td>
<td>-1.5</td>
<td>10.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>72</td>
<td>-2.6</td>
<td>10.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>96</td>
<td>-3.5</td>
<td>10.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>168</td>
<td>-4.1</td>
<td>9.7</td>
<td></td>
</tr>
</tbody>
</table>

### Comparison between Treatment Groups

In both trials, patients treated with Areida had similar response rates in the presence of or absence of bone metastases. Concomitant administration of hormone-sparing treatments did not affect response rates.

Twenty-five patients who had recurrent or relapsing hypercalcemia of malignancy were given a second course of 60 mg of Areida. Of these, 42% showed a complete response and 20% showed a partial response to the second course. Respondents had about a 3 mg/dl fall in mean corrected serum calcium levels 7 days after treatment.

### INDICATIONS AND USAGE

Areida, 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 end-stage renal or non-steroid-induced tumors respond to treatment with Areida. Vascular hypercalcemia is an integral part of hypercalcemia and should be managed 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. Chronic therapy should not be initiated prior to correction of hypercalcemia. The safety and efficacy of Areida in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

### CONTRAINDICATIONS

Areida is contraindicated in patients with clinically significant hyperparathyroidism or to other bisphosphonates.

### WARNINGS

Both rats and dogs, nephropathy has been associated with intravenous, bolus administration of Areida. A 3-month study in rats found cortical tubular changes including epithelial degeneration with intravenous doses at 3 mg/kg, given once every 2 weeks. Following a recovery period (1 month), the degenerative changes were completely reversed. Focal thickenings of renal tubules were partially reversed.

In two studies conducted in dogs, Areida was given as a bolus intravenous injection every 2 weeks for 1 month and once a week for...
3 months. In the 1-month study, tubulo-interstitial 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 hypercalcaemia who receive an intravenous infusion of Arelda should have periodic evaluations of standard laboratory and clinical parameters of renal function.

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

PRECAUTIONS

General
Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphates, magnesium, and potassium should be carefully monitored following infusion of therapy with Arelda. Cases of asymptomatic hyperphosphataemia (19%), hypercalcaemia (9%), hyperphosphatemia (12%) and hypomagnesaemia (12%) were reported in Arelda-treated patients. Cases of symptomatic hypercalcaemia (including tetany) have been reported in association with Arelda therapy. If hypercalcaemia occurs, short-term calcium therapy may be necessary.

Arelda has not been tested in patients who have class D renal impairment (creatinine >3.0 mg/dl). Clinical judgement should determine whether the potential benefits outweigh the potential risk in such patients.

Laboratory Tests
Serum calcium, electrolytes, phosphates, magnesium and creatinine, and CBC, differential, and serum/urine creatinine must be closely monitored in patients treated with Arelda. Patients who have pre-existing renal disease or disturbances of electrolyte balance 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 Arelda.

Cardiogenic, Hysteretic, Impaired or Fertility
In a 104-week cardiogenic study (daily oral administration) in rats, there was a positive dose-response relationship for benign adrenal pheochromocytomas in males (p <0.00001). Although this condition was also observed in humans, the incidence was not statistically significant. When the dose calculations were adjusted to account for the limited oral bioavailability of Arelda in rats, the lowest daily dose associated with adrenal pheochromocytoma was similar to the intended clinical doses. Arelda (daily oral administration) was not cardiogenic in an 80-week study in mice.

Arelda was nonmutagenic in four mutagenicity assays: Ames test, nucleo-anomaly test, sister-chromatid-exchange study, and pre-mutation test.

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

Pregnancy Category C
Arelda 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/kg/day 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 120 mg/kg/day during the period of gestation failed to demonstrate any teratogenic, lethal, or embryotoxic effects in rats or rabbits. Animal reproduction studies have not been conducted with intravenously administered Arelda. It is not known if intravenous Arelda 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. Arelda should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether Arelda is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Arelda is administered to a nursing woman.
Pediatric use
Safety and effectiveness of Areia 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 Areia 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 Areia.
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 2 patients who had hyperostosis of
malignancy-another patient who had Paget's disease of bone
developed Areia. Two men with leptomeningeal and
neurosarcoidosis developed Areia in an uncontrolled study.

Four of 80 (4.9%) who received Areia, during the 2
U.S. controlled hyperostosis 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 19% of patients treated with Areia for hyperostosis 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
Gastrointestinal: Urinary tract infection
Musculoskeletal: Bone pain
Laboratory abnormality: Anemia, hypokalemia, hypomagnesium,
hyperphosphatemia
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.

Bisphosphonates-Related Adverse Experience
in Two U.S. Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Percent of Patients</th>
<th>Areia (91 x 97)</th>
<th>Denosumab (4 x 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 mg</td>
<td>90 mg</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection-site</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Cardiovascular
Atrial Fibrillation 0 6 0
Hypertension 0 6 0
Syncope 0 6 0
Tachycardia 0 6 0
Endocrine System
Hypothyroidism 0 6 0
Hematologic and Lymphatic System
Anemia 0 6 0
Laboratory Abnormalities
Hypocalcemia 2 12 0
Hypercalcemia 4 18 0
Hypomagnesemia 6 12 3
Hypophosphatemia 14 18 3
Abnormal hepatic function 0 0 3

OVERDOSE
One obese woman (95 kg) who was treated with 200 mg of Aredia® daily for 3 days, received the IV dose (38.2°C), hypertension (blood pressure 170/90 mmHg, 90/50 mmHg), and transient tachypnea, noted about 6 hours after the first infusion. The fever and hypertension were rapidly corrected with atenolol.
If overdose occurs, symptomatic hypocalcemia could also occur; such patients should be treated with intravenous calcium.

DOSEAGE AND ADMINISTRATION
Consideration should be given to the severity of as well as the symptoms of hypocalcemia. The recommended dose of Aredia® in moderate hypocalcemia (corrected serum calcium of approximately 10-13.5 mg/dL) is 80-80 mg, and in severe hypocalcemia (corrected serum calcium, <10.5 mg/dL) is 80 mg, given as an initial, single-dose, intravenous infusion over 24 hours. Albumin-corrected serum calcium (CaCl₂, mg/dL) = serum calcium, mg/dL + 0.8 (4.0 - serum albumin, g/dL). Vigorous saline hydration alone may be insufficient for treating mild, asymptomatic hypocalcemia. Overhydration should be avoided in patients who have potential for cardiac failure. In hypocalcemia associated with hemodialysis or hemofiltration, the use of glucocongress 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/mL. The pH of the reconstituted solution is 8.0 - 14. 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 0.9% or 0.45% Sodium Chloride, USP, or 9% Dextrose injection, USP. The infusing solution is stable for up to 24 hours at room temperature. Aredia® must not be mixed with calcium-containing infusions, 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 38-46°F (3-8°C) for up to 24 hours.

HOW SUPPLIED
Vials - each contains 30 mg of sterile, hypophosphonate disodium and 470 mg of mannitol, USP.
Cartons of 4 vials...

Ciba Pharmaceutical Company Division of Ciba-Geigy Corporation
Summit, New Jersey 07901