of phosphate from bone and increased renal excretion as parathyroid hormone levels, which are usually suppressed in hyperparathyroidism, associated with malignancy, return towards normal. Phosphate therapy was administered in 30% of the patients in response to a decrease in serum phosphate levels. Phosphate levels usually returned to normal within 7-10 days.

Urinary calcium excretion and urinary hydroxyproline to creatinine ratios decreased and returned to within or below normal after treatment with Androoster. These changes occur within the first week after initiation, at 6 weeks in serum calcium levels, and are consistent with an antiresorptive pharmacologic action.

Hypercalcemia of Malignancy

Calcium metabolism resulting in sarco- or bone resorption is the underlying pathophysiologic event in metastatic bone disease and hypercalcemia of malignancy. Excessive release of calcium by the bone is the result of hormone or growth factor-induced osteolysis, with progressive destruction and release of bone mineral as well. This, in turn, results in increased renal reabsorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Conversion of excessive bone resorption and adequacy of fluid administration to correct volume deficits are the treatment essential to the management of hypercalcemia.

Most cases of hypercalcemia associated with malignancy occur in patients who have breast cancer, small cell lung cancer 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 rare, nonmalignant conditions, including metastatic extramammary Paget's disease of the breast and rare primary hyperparathyroidism, also may be associated with hypercalcemia. In humoral hypercalcemia, sarco-atechines are activated with bone resorption stimulated by tumor factors such as osteoclast-activating factor, which are excreted by the tumor and detected systemically. Humoral hypercalcemia usually occurs in adenocarcinoma of the lung or head and neck or in parathyroid tumors such as nonmalignant parathyroid or ovarian cancer. Evidence from patients may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to 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 nonmalignant hypercalcemia is commonly present, ideally, limited serum calcium levels should be used to diagnose and tailor hypercalcemia treatments. However, these are not common or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium values for differences in albumin levels is then used in place of measurement of albumin-corrected serum calcium or magnesium in use for this type of treatment (see "DOSAGE AND ADMINISTRATION").

Clinical Trials

In a double-blind clinical trial, 82 patients who had hypercalcemia of malignancy were assigned to receive 30 mg, 60 mg, or 90 mg of Androoster as a single 34-hour intravenous infusion. Their corrected serum calcium levels were 11.5 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 12.6 mg/dL, 13.3 mg/dL and 13.3 mg/dL, respectively.

The majority of patients (84%) had decreased in albumin-corrected serum calcium levels by 31 hours after initiation of treatment. In uncorrected serum calcium levels at 4-7 days after initiation of treatment with Androoster were significantly reduced from baseline in all three dosage groups. As a result, by 7 days after initiation of treatment with Androoster, 40%, 61%, and 100% of the patients receiving 30 mg, 60 mg, and 90 mg of Androoster, respectively, had normal corrected serum calcium levels. Many patients (25-82%) in the 60 mg and 90 mg dosage groups continued to have normal corrected serum calcium levels, in a serial analysis of 1% decrease of corrected serum calcium from baseline, at 6 days.

In a second double-blind, controlled clinical trial, 106 cancer patients who had corrected serum calcium levels of 12.5 mg/dL
A 3-month study in rats found cortical tubular changes including epithelial degeneration with intravenous doses of AMF, 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, Areaza was given as a bolus intravenous injection either daily for 1 month or once a week for 5 months. In the 1-month study, tubulointerstitial nephritis, tubular degeneration and dilatation 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.

after at least 24 hours of saline hydration were randomized to receive either 20 mg of Areaza as a single 24-hour intravenous infusion or 25 mg/kg of Dioctyl sodium sulfosuccinate as a 4-hour intravenous infusion daily for 5 days. Thirty patients were randomly assigned to receive Areaza and 35 to receive Dioctyl sodium sulfosuccinate (Dioctyl).

The mean baseline homocysteine level for the Areaza group and the Dioctyl group was 14.8 mg/dL, and 15.6 mg/dL, respectively.

By day 7, 70% of the patients in the Dioctyl group and 41% of the patients in the Areaza group had normal homocysteine levels (P < 0.01). Among patients, homocysteine levels in the Dioctyl and Areaza groups decreased correspondingly to 5.4 and 11.1 mg/dL, respectively, on day 7. At day 14, 60% of patients in the Dioctyl group and 48% of patients in the Areaza group still had normal homocysteine levels, or measurement of a partial response. The data are summarized in the following table:

<table>
<thead>
<tr>
<th>Time</th>
<th>Areaza (mg/dL)</th>
<th>Dioctyl (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14.8</td>
<td>15.6</td>
</tr>
<tr>
<td>7</td>
<td>5.4</td>
<td>11.1</td>
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<tr>
<td>14</td>
<td>4.0</td>
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</tr>
<tr>
<td>28</td>
<td>3.6</td>
<td>8.2</td>
</tr>
</tbody>
</table>

*Comparison between treatment groups*

In both trials, patients treated with Areaza had a similar response rate in the presence of additional bone metastases. Concomitant administration of lassmacrocines did not affect response rates.

Twenty-five patients who had received or had refractory hypercalcemia with medroxyprogesterone acetate were given a 25 mg/kg. of Areaza. Of these, 40% showed a complete response and 14% showed a partial response to the thalidomide, and those responders had a 2.5 mg/kg dose for at least 3 months, or at least 3 months of 2.5 mg/kg dose for at least 6 months.

### INDICATIONS AND USAGE
Areaza, in association with adequate hydration, is indicated for the treatment of hypercalcemia associated with malignancy, with or without bone metastases. Patients who have either epithelial or non-epithelial tumors should be treated with AREAZA, androgenic or antiandrogenic therapy, and/or hormone therapy. Patients with parathyroid hyperplasia should be treated with parathyroidectomy. The efficacy of Areaza in the treatment of hypercalcemia associated with hyperparathyroidism or with other hypercalcemia-related conditions has not been established.

### CONTRAINDICATIONS
Areaza is contraindicated in patients with known hypersensitivity to Areaza or related compounds.

### WARNINGS
In both rats and dogs, hypercalcemia has been associated with renal function. A high incidence of renal failure has been observed in rats treated with Areaza. In dogs treated with Areaza, increased creatinine clearance and decreased creatinine clearance were observed. The clinical significance of these findings is unknown.
PRECAUTIONS

General
Standard hematological and biochemical parameters, such as serum levels of calcium, phosphorus, magnesium, and potassium should be carefully maintained following initiation of therapy with Anexa. Cases of asymptomatic hypercalcemia (10%), hyperparathyroidism (8%), hyperphosphatemia (12%), and hyperkalemia (8%), were reported in Anexa-treated patients. One death of hypercalcemia with symptoms is likely to have been reported during one Anexa treatment. If hypercalcemia occurs, short-term calcium therapy may be needed.

Anexa has not been tested in patients who have dose less than 2 mg/kg body weight in 24 hours. Clinical judgment should determine whether the potential benefit outweighs the potential risk in such patients.

Dosage and Administration

Anexa is administered to the site of injection and should be injected under sterile conditions.

Dosage

Anexa is injected intramuscularly or subcutaneously at the injection site. The site is marked with the needle point before administration.

Anexa should be stored at room temperature (15°C to 30°C). It should not be frozen.

Pediatric Use

Safety and effectiveness of Anexa in children have not been established.
Drug-related local soft-tissue symptoms (redness, swelling or induration and pain on palpation) at the site of catheter insertion were most common (16%) in patients treated with 80 mg of Arida. When all on-therapy events are considered, that rate rises to 41%. Symptomatic treatment resulted in rapid resolution in all patients.

Four of 82 patients (4.9%) who received Arida during the 2 U.S. controlled hypercalcaemia 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**

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<th>Type</th>
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<th>Denosia (N = 36)</th>
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</thead>
<tbody>
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<td></td>
</tr>
<tr>
<td>Fatigue</td>
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<tr>
<td>Fever</td>
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<td>9</td>
</tr>
<tr>
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<tr>
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<td>0</td>
</tr>
<tr>
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<td>Abnormal hepatic</td>
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<tr>
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</tbody>
</table>
OVERDOSE

One case of a patient (59.0) who was treated with 265 mg of Aredia
for 3 days, 1.0 mg/kg of body weight, for 2 weeks (14 days), resulted in
an increase in serum creatinine of approximately 1.0 mg/dL. This patient
had a history of hypertension and was taking antihypertensive medica-
tions. The patient's blood pressure was elevated before treatment with
Aredia, but it returned to normal after discontinuation of the drug.

If overdose occurs, symptomatic hypocalcemia should also
occur. However, calcium should be treated with adequate calcium
infusion.

*CRADLE AND ADMINISTRATION

Consentation should be given in the presence of as well as the
symptoms of hypocalcemia. The recommended dose of Aredia is
800 mg/m² per week, given at a rate of 20 mg/m² over 4 hours.
The dose should be decreased by 50% in patients with renal insuffi-
cency or dialysis. If hypocalcemia occurs, calcium should be administered
immediately. If symptoms persist, the dose of Aredia may be decreased
or discontinued.

A limited number of patients have received more than one treat-
ment with Aredia. Treatment with Aredia may be continued if hypocalcemia
remains. It is recommended that a minimum of 7 days elapse between treatments, to allow for full
response to the initial treatment. The dose and frequency of treatment
are increased if the initial response is inadequate.

Preparation of Solution

Aredia is reconstituted by adding 10 mL of sterile water for
injection, USP, to each vial, resulting in a solution of 20 mg/mL.
The pH of the reconstituted solution is 3.6-7.4. The drug should
be administered slowly over 4 hours. The daily dose should be administered as one intravenous infusion over
84 hours. The recommended dose should be divided into 1000 mL of
sterile water or 0.9% sodium chloride, USP, or 0.9% dextrose
solution, USP. This infusion solution is stable for up to 24 hours at
room temperature. Aredia must be mixed with diluents
containing substances compatible with Aredia.

Notes:
- Parenteral drug products should be inspected visually
for particulate matter and discoloration. If discoloration
or turbidity is detected, the product should be discarded
and a new vial used.
- Aredia must be mixed with sterile water for injection
before it is reconstituted. The pH of the reconstituted
solution should be 6.5-7.4.

How Supplied

Vials - each contains 50 mg of Aredia, hydrochloride, paracetamol
dihydrate, and 475 mg of mannitol, USP.

Note: Each vial contains 50 mg of Aredia, hydrochloride, paracetamol
dihydrate, and 475 mg of mannitol, USP.

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