Aredia® (multiple brands available)

Pamidronate belongs to a class of bisphosphonates which inhibits osteoclast activity in bone. Pamidronate binds to hydroxyapatite and inhibits osteoclast migration and maturation. In cancer patients with bone metastases and multiple myeloma, lytic bone metastases are caused by increased osteoclast activity. Metastatic tumor cells secrete paracrine factors, which stimulate neighboring osteoclasts to resorb bone. By inhibiting osteoclast function, bisphosphonates interrupt the cascade of events that lead to tumor-induced osteolysis. Pamidronate normalizes serum calcium levels even in tumour induced hypercalcemia without detectable metastases. Pamidronate has been shown to reverse hypercalcemia, prevent or delay skeletal-related events and decrease bone pain.

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Bioavailability</th>
<th>Oral: Low (around 1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Pamidronate has a high affinity for calcified tissues, i.e. bone.</td>
<td></td>
</tr>
<tr>
<td>Cross blood brain barrier?</td>
<td>No information found</td>
<td></td>
</tr>
<tr>
<td>PPB</td>
<td>54 %</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Pamidronate does not appear to be metabolized.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active metabolites</td>
<td>no</td>
</tr>
<tr>
<td>Inactive metabolites</td>
<td>no</td>
</tr>
</tbody>
</table>
Elimination

Pamidronate is excreted intact renally (biphasic elimination). Renal clearance tends to correlate with creatinine clearance. Percentage of dose retained is independent of the dose and infusion rate; accumulation is not capacity limited and is dependent solely on the cumulative dose.

<table>
<thead>
<tr>
<th>Urine</th>
<th>20 - 55 % unchanged in 72 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>α phase: 1.6 h; β phase: 27 h</td>
</tr>
</tbody>
</table>

C - Indications and Status

Health Canada Approvals:

- Tumour-induced hypercalcemia following adequate saline rehydration.
- Conditions associated with increased osteoclast activity: predominantly lytic bone metastases and multiple myeloma.

(Refer to the product monograph for other non-oncology indications.)

D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following table contains adverse effects reported mainly in oncology randomized trials where incidence > placebo.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT* (%)</th>
<th>ONSET**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Atrial fibrillation (2%)</td>
<td>I E</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity (rare)</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>Hypertension (&lt;10%)</td>
<td>I</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Rash (&lt;10%)</td>
<td>E</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain (17%)</td>
<td>E</td>
</tr>
</tbody>
</table>
Anorexia (21%)  E
Dyspepsia (14%)  E
Nausea, vomiting (48%)  I

General  Flu-like symptoms (36%)  I
Hematological  Anemia (<10%)  E  D
Myelosuppression (up to 10%)  E
Hepatobiliary  ↑ LFTs (rare)  E
Hypersensitivity  Hypersensitivity (rare)  I
Infection  Viral (reactivation - rare)  E
Injection site  Injection site reaction (<10%)  I
Metabolic / Endocrine  Abnormal electrolyte(s) (>10%)  E
Musculoskeletal  Fracture (atypical)  D
Musculoskeletal pain (23%) (may be severe)  E
Osteonecrosis of jaw (rare)  L
Nervous System  Cognitive disturbance (rare)  E
Dizziness (rare)  E
Headache (24%)  E
Seizure (rare)  E
Ophthalmic  Conjunctivitis (<10%)  E
Uveitis, scleritis or xanthopsia - rare  E
Renal  Nephrotoxicity (rare)  D
Respiratory  Cough, dyspnea (23%)  E
Pneumonitis / ARDS (rare)  D
Urinary  Urinary tract infection (15%)  E

* "Incidence" may refer to an absolute value or the higher value from a reported range. "Rare" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

Dose-limiting side effects are underlined.

** I = immediate (onset in hours to days)  E = early (days to weeks)  D = delayed (weeks to months)  L = late (months to years)

Adverse reactions with pamidronate are usually mild and transient. The most common adverse reactions are **influenza-like symptoms** and **mild fever**. Acute “influenza-like” reactions may last up to 48 hours and usually occur only with the first pamidronate infusion. Severe musculoskeletal pain has been reported.

**Deterioration of renal function** has been noted with bisphosphonates, although in some cases
patients may have had pre-existing renal dysfunction or be dehydrated.

**Hypocalcemia** has been reported, and is usually asymptomatic, but may be more common in patients with prior thyroid surgery.

**Osteonecrosis of the jaw** has been reported with an increased risk in patients who smoke, have comorbid or dental diseases, poorly fitting dentures, have had invasive dental procedures, are receiving steroids, radiotherapy, chemotherapy, or parenteral bisphosphonate formulations. Patients should be advised to have dental examinations prior to starting therapy and to avoid invasive dental procedures on treatment. The start of treatment or a new course of treatment should be delayed in patients with unhealed, open soft tissue lesions in the mouth. In multiple myeloma patients, consider discontinuing treatment after 2 years for stable responding patients, or decreasing the frequency to every 3 months.

**Atypical fractures of the femur** (subtrochanteric or diaphyseal) have been reported with bisphosphonate use, primarily in patients receiving long-term treatment. These fractures are often bilateral, occur with minimal or no trauma, with symptoms including thigh or groin pain. Imaging features of stress fractures may be seen weeks to months before presentation with a completed femoral fracture. Poor healing of these fractures has also been reported.

---

**E - Dosing**

Refer to protocol by which patient is being treated.

Patients (especially those with hypercalcemia) must be adequately hydrated before and during treatment, but overhydration should be avoided especially in patients with cardiac disease. Delay treatment in patients with unhealed soft tissue mouth lesions.

**Do not administer doses over 90mg or exceed the recommended infusion rate.**

Calcium and vitamin D supplements should be given to patients at risk of low serum calcium and who have no history of hypercalcemia.

**Adults:**

- **Tumor induced hypercalcemia (TIH):**
  - Rehydration with normal saline before treatment is mandatory.
<table>
<thead>
<tr>
<th>Initial Serum Calcium*(mmol/L)</th>
<th>Total dose over 3-4 weeks (mg)</th>
<th>IV Infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 3</td>
<td>30</td>
<td>22.5 mg/h</td>
</tr>
<tr>
<td>&gt; 3 – 3.5</td>
<td>30 or 60</td>
<td>22.5 mg/h</td>
</tr>
<tr>
<td>&gt; 3.5 - 4</td>
<td>60 or 90</td>
<td>22.5 mg/h or 4 h</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>90</td>
<td>22.5 mg/h or 4 h</td>
</tr>
</tbody>
</table>

*use corrected calcium levels, calculated using the following formula:

Corrected Calcium (mmol/L) = Measured Calcium (mmol/L) + (0.02X[40-Measured Albumin (g/L)])

Bone metastases:
**Intravenous**: 90 mg over 2 hours every 4 weeks
(or Q 3 week at dose of 90 mg with scheduled chemotherapy)

Multiple Myeloma:
**Intravenous**: 90 mg over 4 hours every 4 weeks

**Dosage with Toxicity:**

Dosage in myelosuppression: No dosage adjustment required.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteonecrosis of jaw</td>
<td>Refer patient to dentist or dental surgeon; hold until recovery.</td>
</tr>
<tr>
<td>Atypical fractures of the femur</td>
<td>Consider discontinuing</td>
</tr>
<tr>
<td>Severe musculoskeletal pain</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Ocular symptoms other than uncomplicated conjunctivitis</td>
<td>Refer to ophthalmologist; consider discontinuing.</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Hold until recovered to within 10% of baseline</td>
</tr>
</tbody>
</table>

**Dosage with Hepatic Impairment:**

AUC is increased in mild to moderate hepatic impairment but not considered clinically relevant; no dosage adjustment is required. No data available in patients with severe hepatic impairment.
**Dosage with Renal Impairment:**

Patients with severe renal impairment (< 30mL/min) have 3 times higher pamidronate exposure than those with normal renal function.

<table>
<thead>
<tr>
<th>Baseline Level</th>
<th>Action</th>
<th>During Treatment Level/change</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clcr &gt; 90 mL/min</td>
<td>No adjustment needed</td>
<td>Creatinine ↑ of 44 µmol/L if normal baseline</td>
<td>Hold until returns to within 10% of baseline</td>
</tr>
<tr>
<td>Clcr 30-90 mL/min</td>
<td>Use 4 hour infusion</td>
<td>Creatinine ↑ of 88 µmol/L if abnormal baseline</td>
<td></td>
</tr>
<tr>
<td>Clcr &lt; 30 mL/min or Creatinine &gt; 440 µmol/L (TIH) or &gt; 180 µmol/L (myeloma)</td>
<td>Only use for life-threatening hypercalcemia where the benefit exceeds risk</td>
<td>Clcr &lt; 30 mL/min or Creatinine &gt; 440 µmol/L (TIH) or &gt; 180 µmol/L (myeloma)</td>
<td>Only use for life-threatening hypercalcemia where the benefit exceeds risk</td>
</tr>
</tbody>
</table>

**Dosage in the elderly:**

No data available.

**Children:**

Safety and efficacy not established. Not recommended for use in children.

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F - Administration Guidelines

- Pamidronate must not be mixed with calcium-containing solutions.
- Mix in 250-500mL solution (D5W or NS) and infuse over 2-4 hours (Use the higher range of infusion volume and duration if renal impairment, tumour-induced hypercalcemia or myeloma). Never exceed 1 mg/minute.
- May infuse using ambulatory infusion device over 2-4 hours.
- Pamidronate must never be given as a bolus injection because of the risk of thrombophlebitis, severe local reactions and renal failure; it should always be diluted and administered as a slow IV infusion.
- All patients, especially those who are dehydrated or hypercalcemic, must be adequately rehydrated prior to treatment with pamidronate.
- Admixed solutions are chemically and physically stable for 24 h at 2-8°C, protected from light, followed by 24h at room temperature, exposed to light (total 48h stability).

G - Special Precautions

Contraindications:

- Patients with known or suspected hypersensitivity to pamidronate, or any of its components, or to other bisphosphonates.
- Pamidronate should not be given together with other bisphosphonates to treat hypercalcemia, since the combined effects of these agents are unknown.

Other Warnings/Precautions:

- Patients must be adequately hydrated throughout treatment, but special care should be taken in the elderly and patients with cardiac disease, to prevent fluid overload and cardiac failure.
- Avoid in patients with severe renal impairment, except in life-threatening cases of hypercalcemia.
- Use with caution in patients with risk factors for ONJ (see adverse effects description section)

Other Drug Properties:

- Carcinogenicity: No

Pregnancy and Lactation:

- Mutagenicity: No
- Fetotoxicity: Yes
Teratogenicity: Yes
Pamidronate is contraindicated for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose (general recommendation).

Excretion into breast milk: Yes
Breastfeeding is not recommended.

Fertility effects: Probable

H - Interactions

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxic drugs</td>
<td>Renal impairment</td>
<td>Additive</td>
<td>Avoid, use with caution</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Renal impairment</td>
<td>Unknown</td>
<td>Caution</td>
</tr>
</tbody>
</table>

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental examination with appropriate preventative dentistry before starting treatment. Regular dental check- ups and avoidance of invasive dental surgery during treatment.</td>
<td></td>
</tr>
<tr>
<td>Electrolytes, including corrected serum calcium, phosphates, magnesium, and serum albumin</td>
<td>Baseline and as clinically indicated</td>
</tr>
<tr>
<td>Renal function tests and fluid balance (urine output, daily weights), especially in patients with pre-existing renal disease or risk of renal impairment</td>
<td>Baseline and at each visit</td>
</tr>
<tr>
<td>Clinical toxicity assessment (including flu-like syndrome, hypersensitivity, hydration, pain, dental and ocular effects)</td>
<td>At each visit</td>
</tr>
</tbody>
</table>

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events)
Suggested Clinical Monitoring

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, in patients with anemia, leukopenia, or thrombocytopenia</td>
<td>Baseline and at each visit</td>
</tr>
</tbody>
</table>

J - Supplementary Public Funding

New Drug Funding Program ([NDFP Website](http://www.ndfpwebsite.com))
- Pamidronate - Metastatic Breast Cancer
- Pamidronate - Plasma Cell Myeloma (with bone disease)
- Pamidronate - Plasma Cell Myeloma (without bone disease)

K - References

CCO Practice Guideline: [Use of Bisphosphonates in Women with Breast Cancer](http://www.ccoformulary.com)

CCO Practice Guideline: The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma


Product Monograph: Zometa® (zoledronic acid). Novartis Pharmaceuticals, March 5, 2012.
L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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