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A DRUG NAME: PAMIDRONATE

SYNONYM(S): APD, Disodium Pamidronate

COMMON TRADE NAME(S): Aredia® (Novartis Pharmaceuticals), Pamidronate Injection® (Sandoz, Hospira, Pharmaceutical Partners of Canada)

B MECHANISM OF ACTION AND PHARMACOKINETICS

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.

Oral Absorption	Low (around 1%)	
Distribution	Pamidronate has a high affinity for calcified tissues, i.e. bone	
	Cross blood brain barrier?	No information found
	PPB	54%
Metabolism	Pamidronate does not appear to be metabolised.	
	Active metabolite(s)	No
	Inactive metabolite(s)	No
Excretion	Pamidronate is excreted intact renally. 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.	
	Urine	20-55% unchanged in 72 hrs
	Plasma T _{1/2}	0.8 hours

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C INDICATIONS AND STATUS

- * Tumour-induced hypercalcemia following adequate saline rehydration.
- * Conditions associated with increased osteoclast activity: predominantly lytic bone metastases and multiple myeloma.
- * Symptomatic Paget's disease of bone

- * *Health Canada approved indication*

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D ADVERSE EFFECTS (In Randomized Trials where Incidence > Placebo)

ORGAN SITE	SIDE EFFECT	ONSET
Central Nervous System	Dizziness, seizures (rare)	E
	Altered level of consciousness (rare)	E
	Visual hallucinations, confusion (rare)	E
	Sleep disorders	E
	Headache (24%), agitation	E
Dermatological	Pruritus (rare), rash (common)	E
Extravasation hazard (refer to Appendix 2)	Mild Irritant (2%)	
Gastrointestinal	Dyspepsia (14%)	E
	Anorexia (21%)	E
	Anorexia, abdominal pain (17%)	E
	Nausea or vomiting (48%)	I
General	Fever, flu-like syndrome (36%)	I
	Conjunctivitis, uveitis / xanthopsia (rare)	E
	Reactivation herpes (rare)	E
	Hypersensitivity (rare)	I
Hematologic	Anemia (35%)	E
	Hypocalcemia (3%), ↑ sodium (rare)	E
Metabolic	↓ Mg, K, phosphate (rare)	E
	Abnormal LFT's (rare)	E
Musculoskeletal	Myalgia /arthralgia (23%)	E
	Osteonecrosis of jaw	L

D	ADVERSE EFFECTS (In Randomized Trials where Incidence > Placebo) - Continued		
	ORGAN SITE	SIDE EFFECT	ONSET
	Renal	<u>Glomerulosclerosis</u> (rare)	D
		Hematuria (rare), <u>Acute renal failure</u>	D
	Cardio-Respiratory	Cough / dyspnea (23%)	E
		Cardiac failure (rare), hypo/hypertension	I
		ARDS / pneumonitis (rare)	I

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** (an increase of temperature of > 1° C, which may last up to 48 hours). Fever usually resolves spontaneously and does not require treatment. Acute “influenza-like” reactions 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. The role of pamidronate in changes of renal function in patients without pre-existing renal dysfunction is unclear, thus merits cautious observations.

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, especially in patients also receiving steroids, radiotherapy, and chemotherapy who have had invasive dental surgery. The onset can occur from months to years after the start of bisphosphonate therapy. Patients should be advised to have dental examinations prior to starting therapy and to avoid invasive dental procedures while receiving pamidronate. In multiple myeloma patients, consider either discontinuing treatment after 2 years for stable responding patients or decreasing frequency to three monthly.

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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. Do not administer doses over 90mg. Consider calcium/ vitamin D supplements in patients who are not at risk of hypercalcemia.

Adults:

Tumor induced hypercalcemia (TIH): Rehydration with normal saline before treatment is mandatory.

E DOSING (continued)

Initial Serum Calcium* (mmol/L)	Total dose over 3-4 weeks (mg)	Infusion rate
Up to 3.0	30	22.5mg/ hr
> 3.0 – 3.5	30 or 60	22.5mg/ hr
> 3.5 - 4.0	60 or 90	22.5mg/ hr or 4 hrs
> 4.0	90	over 4 hours

Bone metastases: Q 4 week: 90mg in 250mL over 2 hours
(or Q 3 week at dose of 60-90 mg with scheduled chemotherapy)

Multiple Myeloma Q 4 weeks: 90mg in 500mL over 4 hours

Dosage in myelosuppression: No dosage adjustment required.

Dosage with renal impairment:

Creatinine		Creatinine Clearance (mL/min)	Action
Normal	Or	> 60	No dose adjustment necessary
Normal	Or	30-90	4 hour infusion rate recommended
Increases on treatment	Or	<30	Hold dose, especially with myeloma or breast cancer patients Use only for severe hypercalcemia with extreme caution

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 dysfunction.

Children: Safety and efficacy not established.

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F ADMINISTRATION GUIDELINES (see [Appendix 3b](#))

- 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, TIH or myeloma). Never give > 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 phlebitis; it should always be diluted and administered as a slow IV infusion.
- Dehydrated patients must be adequately rehydrated prior to treatment with pamidronate.

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* Should use corrected Calcium levels, calculated using the following formula:
Corrected Calcium (mmol/L) = Measured Calcium (mmol/L) + (0.02X[40-Measured Albumin (g/L)])

G SPECIAL PRECAUTIONS

Pamidronate is **contraindicated** in patients with known or suspected hypersensitivity to pamidronate, or any of its components, or to other biphosphonates. Pamidronate should not be given together with other bisphosphonates to treat hypercalcemia since the combined effects of these agents are unknown.

Patients must be adequately hydrated throughout treatment, but special care should be taken in the elderly, and those patients with cardiac disease, to prevent fluid overload and cardiac failure.

Pamidronate crosses the placenta, accumulates in fetal bone and is fetotoxic, but is not teratogenic, mutagenic or carcinogenic. Pamidronate is excreted into breast milk; therefore, it is **contraindicated** in **pregnancy** and **lactation**. Pamidronate reduces fertility in both sexes. Adequate contraception must be used by both sexes during treatment, and for at least 6 months following the last dose of pamidronate.

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H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
Nephrotoxic drugs	Renal impairment	Additive effects	Avoid, use with caution
Thalidomide	Renal impairment	Unknown	Use with caution

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I RECOMMENDED CLINICAL MONITORING**Recommended Clinical Monitoring**

- Clinical toxicity assessment (including flu-like syndrome, hydration, pain, dental). Grade toxicity using the current [NCI Common Toxicity Criteria Version](#)
- Baseline and regular serum creatinine
- Baseline and periodic corrected serum calcium, phosphate, electrolytes, magnesium, and serum albumin
- Dental examination with appropriate preventative dentistry should be considered prior to treatment. Regular dental check-ups. Avoid invasive dental surgeries while on treatment.

Suggested Clinical Monitoring

- Baseline and regular CBC in patients with anemia

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CCO Practice Guideline: [Use of Bisphosphonates in Patients with Bone Metastases from Breast Cancer](#)

CCO Practice Guideline: [The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma](#)

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