DRUG NAME: Pamidronate

SYNONYM(S): Pamidronate disodium, pamidronic acid, APD, aminohydroxypropylidene bisphosphonate

COMMON TRADE NAME(S): AREDIA®

CLASSIFICATION: Bone metabolism regulator

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Pamidronate is a second-generation bisphosphonate, which inhibits bone resorption.[1] Bisphosphonates are analogues of endogenous pyrophosphate and characterized by a P-C-P bond, which is resistant to enzymatic hydrolysis.[2] The mechanism of action of bisphosphonates has not been fully elucidated. Available data suggests that they bind strongly to hydroxyapatite crystals in the bone matrix, preferentially at the sites of increased bone turnover and inhibit the formation and dissolution of the crystals. Other actions of matrix-bound bisphosphonates may include direct inhibition of mature osteoclast function, promotion of osteoclast apoptosis and interference with osteoblast-mediated osteoclast activation.[3] Pamidronate does not interfere with bone mineralization at therapeutic doses.[1] On a molar basis, pamidronate is 10 times more potent than clodronate.[2] In tumour-induced hypercalcemia, bone resorption is increased in the presence of neoplastic tissue. Pamidronate inhibits abnormal bone resorption and reduces the flow of calcium from the resorbing bone into the blood, thus, decreasing total and ionized serum calcium. In the treatment of osteolytic bone metastases in breast cancer and multiple myeloma, pamidronate helps reducing morbidity of bone metastases by inhibiting accelerated bone resorption induced by the tumour.[4]

PHARMACOKINETICS:

Interpatient variability	no information found	
Oral Absorption	<1% absorbed[5]	
Distribution	45-53% is adsorbed to bone in the areas of high turnover after an intravenous dose of 60 mg infused over 24 hours.[4] Body retention of pamidronate correlates with the number of bone metastases in patients with cancer.[3]	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	54%[4]
Metabolism	does not appear to be metabolized	
	active metabolite(s)	none
	inactive metabolite(s)	none
Excretion	renal excretion; there is a tendency for renal clearance to correlate with creatinine clearance.	
	urine	20-55% as unchanged drug within 72 hours
	terminal half life	27 hours
	clearance	180 mL/min

Adapted from reference[6] unless specified otherwise

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USES:

Primary uses:

*Tumour-induced hypercalcemia[7-9]

*Osteolytic bone metastases[11-15]

Other uses:

Bone loss due to androgen suppression in prostate cancer[10]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to to pamidronate or other bisphosphonates[4,6]

Caution:

- ***Hydration:*** In the treatment of acute tumour-induced hypercalcemia, patients must be adequately hydrated with intravenous NS (0.9% NaCl) before and during pamidronate therapy to expand intracellular volume and to increase renal calcium clearance.[7,9] The optimum infusion rate of NS should be determined by the severity of hypercalcemia, the degree of dehydration and the ability of the patient to tolerate fluid. Infusion rate of 200-300 mL/h has been commonly used. However, these infusion rates may require adjustment if signs and symptoms of fluid overload occur.[9]

Carcinogenicity: Studies on rats and mice did not find pamidronate to have carcinogenic potential.[6]

Mutagenicity: Pamidronate was not mutagenic in Ames test, mammalian *in vitro* mutation test or mammalian *in vivo* chromosome test.[6]

Fertility: No information found.[4]

Pregnancy: FDA Pregnancy Category C.[4] Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk.[6]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important (reference expert reviewer). When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group except where indicated.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow/ febrile neutropenia	anemia* (35%)
	granulocytopenia* (17%)
	lymphocytopenia (1-10%)
	thrombocytopenia* (11%)
constitutional symptoms	asthenia* (16%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	fatigue* (30%)
	fever (36%)
dermatology/skin	*extravasation hazard:* none
	injection site reaction (2%)
gastrointestinal	*emetogenic potential:* nonemetogenic
	anorexia* (21%)
	constipation* (28%)
	diarrhea* (24%)
	dyspepsia* (14%)
	nausea* (48%)
	vomiting* (31%)
infection	upper respiratory infection* (20%)
	urinary tract infection* (15%)
metabolic/laboratory	hypocalcemia (3%)
	hypomagnesemia (1-10%)
	hypophosphatemia (>10%)
musculoskeletal	osteonecrosis of the jaw (rare)[16-18]
neurology	insomnia* (18%)
ocular/visual	conjunctivitis (rare)[15]
	uveitis (rare)[15]
pain	abdominal pain* (17%)
	headache* (24%)
	myalgia (23%)
	skeletal pain (59%)
pulmonary	cough* (21%)
	dyspnea* (23%)
syndromes	flu-like symptoms (>10%)

Adapted from reference[6] unless otherwise specified.
*The incidences of these side effects are comparable to those of placebo group.

Fever is a transient febrile reaction with > 1°C elevation in body temperature and may last up to 48 hours.[6] The fever usually occurs within 5 days of the first infusion of pamidronate and it may be accompanied by myalgia, nausea and headache.[3] It is usually self-limiting and does not require treatment.[6] If treatment is needed, acetaminophen may be used. Reducing the infusion rate is usually not helpful.[3]

Symptomatic ***hypocalcemia*** is rare[3] and the symptoms include abdominal cramps, confusion, muscle spasms, lethargy and irritability.[4,19] Patients who have undergone thyroid surgery may be more prone to develop

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hypocalcemia after pamidronate therapy and should be monitored closely.[6,19] Symptomatic hypocalcemia can be treated with oral or intravenous calcium supplement.[6,19]

Osteonecrosis of the jaw (ONJ) is a rare, but serious event that has been associated with antiresorptive agents such as bisphosphonate therapy. Osteonecrosis of other anatomical sites (e.g., femur, hip, auditory canal, metatarsal bones, etc.) have also been rarely reported.[20] ONJ is more commonly observed with increasing bisphosphonate potency, dose intensity, and duration of treatment, particularly when treatment exceeds four years.[21-23] The risk of ONJ is higher with intravenous than with oral bisphosphonate treatment.[24,25] Multiple risk factors may play a role, including invasive dental procedures and pre-existing dental disease,[23,26] concomitant therapy with angiogenesis inhibitors, corticosteroids, and radiation to the head and neck[22-25], as well as certain comorbid medical conditions (e.g., anemia[24,26], cancer[22,25], coagulopathies[24], and diabetes[22,27]). For further details and management of ONJ, refer to *Bisphosphonates and Osteonecrosis of the Jaw in* ***Oral & Dental Care: Osteonecrosis of the Jaw***.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
calcium- or vitamin D-containing preparations[4]	may antagonize the effect of pamidronate in the treatment of hypercalcemia	additive	avoid concurrent therapy

SUPPLY AND STORAGE:

Injection:

Fresenius Kabi Canada Ltd. supplies pamidronate as 30 mg (10 mL), 60 mg (10 mL), and 90 mg (10 mL) single-dose (preservative free) ready-to-use vials in a concentration of 3 mg/mL, 6 mg/mL, and 9 mg/mL respectively. Store at room temperature.[28]

Omega Laboratories Limited supplies pamidronate as 60 mg (10 mL) and 90 mg (10 mL) single-dose (preservative free) ready-to-use vials in a concentration of 6 mg/mL and 9 mg/mL respectively. Store at room temperature.[29]

Pfizer Canada ULC supplies pamidronate as 30 mg (10 mL), 60 mg (10 mL), and 90 mg (10 mL) single-use (preservative free) ready-to-use vials in a concentration of 3 mg/mL, 6 mg/mL, and 9 mg/mL respectively. Store at room temperature.[30]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: It is recommended that pamidronate not be mixed with calcium-containing infusion solutions, such as Ringer's solution.[6]

***Compatibility*:** consult detailed reference

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PARENTERAL ADMINISTRATION:

BC Cancer administration standard noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	not recommended since local reaction and thrombophlebitis may result from high local concentrations[6]
Intermittent infusion	***over 1 h***[31-36]; can also be given over 2-4 h[6,11,12,30] • 90 mg has been safely given over 1 h in patients with mild to moderate renal impairment[31,36]; although longer infusion times (e.g., 90 mg over 4 h) may also be used[28-30] ***Refer to protocol by which patient is being treated.***
Continuous infusion	over 24 hours[4,37]
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3-6 weeks***[6,11,12,38]***:***	***90 mg IV for one dose on day 1*** (total dose per cycle 90 mg)
	4-6 weeks[39,40]***:***	***30 mg IV for one dose on day 1*** (total dose per cycle 30 mg)
	6 months[41,42]***:***	***90 mg IV for one dose on day 1*** (total dose per cycle 90 mg)
	12 weeks[43]:	90 mg IV for one dose on day 1 (total dose per cycle 90 mg)
For bone loss	12 weeks[10]:	***60 mg IV for one dose on day 1***
Dosage in renal failure:	mild to moderate impairment (CrCl 30-90 mL/min): no dose adjustment required[28-30]; pamidronate 90 mg has been safely given over 1 h,[31,36] although longer infusion times (e.g., 90 mg over 4 h) may also be used[28-30] severe impairment (CrCl <30 mL/min): avoid use if possible as there is limited experience with serum creatinine 180-440 micromol/L[28-30]	

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BC Cancer usual dose noted in ***bold, italics***

Cycle Length:

calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: mild to moderate impairment: no adjustment required[28-30]
severe impairment: no information found

Dosage in dialysis no information found

Children:

Intravenous: 1-2 mg/kg IV over 3-24 hours has been used for tumour-induced hypercalcemia[45]

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