Drug Monograph

A - Drug Name

pamidronate

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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.

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 metabolized.	
	Active metabolites	no
	Inactive metabolites	no
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.	
Urine	20 - 55 % unchanged in 72 h
Half-life	α phase: 1.6 h; β phase: 27 h

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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.)

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: None

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

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (2%)	I E
	Cardiotoxicity (rare - due to fluid overload)	D
	Hypertension (<10%)	I
	Hypotension (rare)	I
Dermatological	Rash (<10%)	E
Gastrointestinal	Abdominal pain (17%)	E
	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%) (including ↓Ca, PO4, K, or Mg)	E
Musculoskeletal	Fracture (atypical)	D
	Musculoskeletal pain (23%) (may be severe)	E
	Osteonecrosis of external ear canal (rare)	L
	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.

** 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.

Osteonecrosis of external auditory canal has been observed in patients on long-term bisphosphonate therapy. Possible risk factors include steroid use, chemotherapy, and/or local infection or trauma. Consider the possibility of osteonecrosis of external auditory canal in patients who present with otic symptoms such as chronic ear infections.

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

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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 especially in patients with cardiac disease.

Delay treatment in patients with unhealed soft tissue mouth lesions.

Do not administer doses over 90 mg 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.

Initial Serum Calcium*(mmol/L)	Total dose over 3-4 weeks (mg)	Maximum IV Infusion rate
Up to 3	30	22.5 mg/h
> 3 - 3.5	30 or 60	22.5 mg/h
> 3.5 - 4	60 or 90	22.5 mg/h (i.e. 90 mg/4 h)
> 4	90	22.5 mg/h (i.e. 90 mg/4 h)

*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.

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

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 and so should be used with caution.

Dosage with Renal Impairment:

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

Baseline		During Treatment	
Level	**Action**	**Level/change**	**Action**
Clcr > 90 mL/min	No adjustment needed	Creatinine ↑ of 44 µmol/L if normal baseline	Hold until returns to within 10% of baseline
Clcr 30-90 mL/min	Do not exceed infusion rate of 22.5 mg/h	Creatinine ↑ of 88 µmol/L if abnormal baseline	
Clcr < 30 mL/min or Creatinine > 440 µmol/L (TIH) or > 180 µmol/L (myeloma)	Only use for life-threatening hypercalcemia where the benefit exceeds risk	Clcr < 30 mL/min or Creatinine > 440 µmol/L (TIH) or > 180 µmol/L (myeloma)	Only use for life-threatening hypercalcemia where the benefit exceeds risk

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 (e.g., Ringer's solution).
- Pamidronate is generally mixed in 250-500mL solution (D5W or NS) and infused IV over 2-4 hours (refer to Dosing section).
- According to the product monograph, it is recommended not to exceed 90 mg in 500 mL over 4 hours (i.e. 22.5 mg/h infusion rate) in multiple myeloma and tumour-induced hypercalcemia.
- 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.
- Store unopened vials at room temperature (15-25°C). Protect vials from heat.

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G - Special Precautions

Contraindications:

- Patients with known or suspected hypersensitivity to pamidronate, or any of its components, or to other bisphosphonates
- Pregnant and/or breastfeeding women

Other Warnings/Precautions:

- 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 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).
- Patients should not drive, operate machinery or perform tasks that require alertness if they experience somnolence and/or dizziness after infusion.

Other Drug Properties:

- Carcinogenicity: No

Pregnancy and Lactation:

- Mutagenicity: No
- Fetotoxicity: Yes
  Pamidronate can cause bone mineralization defects during organogenesis in animals.
- 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).
- Breastfeeding: Contraindicated
- Fertility effects: Probable

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Anti-angiogenic drugs	↑ risk of ONJ	Additive	Caution
Calcitonin	Significant ↓ in Ca	Synergistic	Caution
Nephrotoxic drugs	Renal impairment	Additive	Avoid, use with caution
Thalidomide	Renal impairment	Unknown	Caution

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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

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

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
CBC, in patients with anemia, leukopenia, or thrombocytopenia	Baseline and at each visit

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K - References

CCO Practice Guideline: Use of Bisphosphonates in Women with Breast Cancer.

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

Fitton A, McTavish D. Pamidronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. Drugs 1991;41(2):289-318.

Ifosfamide: AHFS Drug Information [Internet]; 2010 [cited 2012 April 4].

Lacy MO, Dispenzieri A, Gertz MA, et al. Mayo Clinic consensus statement for the use of bisphosphonates in multiple myeloma. Mayo Clin Proc 2006;81(8):1047-53.

Product Monograph: Pamidronate disodium for injection. Hospira Healthcare Corp. Mar 30, 2017.

Product Monograph: Pamidronate disodium for injection. Pfizer Canada, Dec 11, 2018.

Product Monograph: Pamidronate disodium for injection. Fresenius Kabi Canada Ltd., March 12, 2019.

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

January 2024 Modified Dosing and Administration guidelines sections

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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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