

Drug Monograph

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A - Drug Name

zoledronic acid

SYNONYM(S): Zoledronate**COMMON TRADE NAME(S):** Zometa®[back to top](#)**B - Mechanism of Action and Pharmacokinetics**

Zoledronic acid is a bisphosphonate, which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors. It binds to hydroxyapatite and accumulates in bone, thus inhibiting osteoclast migration and maturation. Zoledronic acid inhibits skeletal calcium release induced by tumours, and has a clinically significant impact on mixed and osteoblastic metastases in patients with breast or prostate cancer. Preclinical data suggest that zoledronic acid may have pro-apoptotic or cytostatic properties on cancer cells, or anti-angiogenic effects on endothelial cells.

Absorption	Exposure linearly related to dose. Japanese female patients had higher exposure (47%) than the North American population.	
Distribution	Zoledronic acid has a high affinity for calcified tissues i.e. bone. Can be detected in plasma for up to 28 days post-dose.	
	Cross blood brain barrier?	No information found
	PPB	55%
Metabolism	Zoledronic acid does not undergo metabolism and does not affect cytochrome P450 enzymes.	
	Active metabolites	no
	Inactive metabolites	no

Elimination	Zoledronic acid is excreted renally as intact drug; the remaining is bound to bone tissue and released slowly into the systemic circulation. Renal clearance correlates with creatinine clearance in patients with mild-moderate renal failure. Body weight, gender, and race do not cause significant variabilities on clearance.	
	Feces	<3%
	Urine	39% (unchanged in 24 hours)
	Half-life	Terminal: 146 hours

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C - Indications and Status

Health Canada Approvals:

- Treatment of tumour-induced hypercalcemia (corrected serum calcium ≥ 3 mmol/L) following adequate saline rehydration. Prior to treatment with zoledronic acid, renal excretion of excess calcium should be promoted by restoring and maintaining adequate fluid balance and urine output.
- Treatment of patients with documented bone metastases from solid tumours and patients with osteolytic lesions of multiple myeloma in conjunction with standard care in order to prevent or delay potential complication from the bone lesions.

Other Uses:

- Adjuvant Breast Cancer

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: Irritant

The following table contains adverse effects reported mainly in bone metastases trials in patients with solid tumours, where the incidence is higher than in placebo.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (includes atrial fibrillation; rare)	E
	Hypotension (<1%) (rarely severe)	I E
Dermatological	Rash (rare)	I
Gastrointestinal	Diarrhea (24%)	E
	Nausea, vomiting (46%)	E
	Weight loss (16%)	E
General	Edema (21%)	E
	Fatigue (39%)	E
	Flu-like symptoms (acute phase reaction; common)	E
Hematological	Anemia (5%) (↑ from placebo observed)	E
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Injection site reaction (rare)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (10%) (↓Ca, K, Mg, PO4)	E
Musculoskeletal	Fracture (rare)	D
	Musculoskeletal pain (23%) (including arthritis, may be severe)	E
	Osteonecrosis of jaw (2%) (and other sites)	L
Nervous System	Cognitive disturbance (1%)	E
	Depression (14%)	E
	Dizziness (18%)	E
	Headache (19%)	E
	Paresthesia (15%)	E
Ophthalmic	Conjunctivitis (1-10%)	E
	Eye disorders (blurred vision, uveitis, episcleritis; rare)	E
Renal	Nephrotoxicity (17%)	E
	Other acquired Fanconi syndrome (rare)	E D
Respiratory	Bronchospasm (in ASA sensitive asthmatics; theoretical)	E
	Cough, dyspnea (27%)	E
	Pneumonitis (rare)	E D

* "*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)

The most common side effects for zoledronic acid include transient flu-like symptoms, nausea/vomiting, musculoskeletal pain, diarrhea, fatigue, edema, headache, dizziness, renal impairment and cough/dyspnea.

Deterioration of **renal function** has been noted with zoledronic acid. Factors that may increase the potential of deterioration include pre-existing renal impairment, concomitant use of nephrotoxic drugs, dehydration, prolonged exposure to bisphosphonates, zoledronic acid doses > 4mg, or using an infusion time shorter than the recommendations (in 100mL diluent over 15 minutes). Cases of **acquired Fanconi syndrome** have been reported and signs include hyperaminoaciduria, glucosuria in the presence of normal serum glucose, phosphate wasting and other clinical features. If this develops, zoledronic acid should be discontinued and the patient treated appropriately.

Hypocalcemia has been reported, and is usually asymptomatic, but may be severe (e.g. tetany, QTc changes) and has a variable onset time. It may be more common in patients with prior thyroid surgery.

An **acute phase reaction** is common, with symptoms such as fever, fatigue, bone pain and/or arthralgias, myalgias, arthritis, joint swelling and flu-like illness. These reactions usually appear within 3 days after the dose and usually resolve within a few days.

Musculoskeletal pain may occur from days to months after starting treatment and may sometimes be severe. These symptoms recurred in some patients who were re-challenged with the same or different bisphosphonates.

Osteonecrosis of the jaw (ONJ) has been reported, especially in patients also receiving steroids, radiotherapy, anti-angiogenic drugs and chemotherapy who have had invasive dental surgery. Risk may also be increased in those with co-morbid conditions (e.g. anemia, coagulopathies), periodontal and other dental diseases, poorly fitting dentures and smokers. A higher frequency has been reported in advanced breast cancer or multiple myeloma patients. 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 zoledronic acid. The start of treatment should be delayed in patients with unhealed open soft tissue mouth lesions. In multiple myeloma patients, consider either discontinuing treatment after 2 years for stable responding patients or decreasing frequency to every three months. Cases of osteonecrosis of other anatomical sites, including the femur, hip, humerus, external auditory canal, tibia, ribs, spine, knee, and metatarsal bones have been reported post-market in patients treated with zoledronic acid.

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 features 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. Do not combine with other bisphosphonates. Hypocalcemia must be corrected before administering zoledronic acid. All patients should be adequately hydrated prior to and during treatment with zoledronic acid, but overhydration should be avoided especially in patients with cardiac risk factors.

Doses > 4mg should be avoided, due to the increased risk of nephrotoxicity.

Do not administer to patients with open soft tissue lesions in the mouth.

In patients without hypercalcemia (current or history of), oral calcium 500mg and at least Vitamin D 400 IU daily supplements are recommended.

Adults:

Tumour induced hypercalcemia (TIH)¹:

- 4mg IV infusion over ≥ 15 minutes following rehydration
- May retreat after 7 days if not normocalcemic² and can tolerate hydration (3 to 5 litres per day)

¹ Corrected calcium ≥ 3 mmol/L

² Should use corrected calcium levels, calculated using the following formula:

$$\text{Corrected Calcium (mmol/L)} = \text{Measured Calcium (mmol/L)} + (0.02 \times [40 - \text{Measured Albumin (g/L)}])$$

Bone metastases and Multiple Myeloma:

- 4mg IV infusion over ≥ 15 minutes every 3 to 4 weeks

Dosage with Toxicity:

Dosage in myelosuppression: No dosage adjustment required

Toxicity	Action
Atypical fractures of the femur	Hold if suspected. Consider discontinuing if confirmed.
Ocular symptoms other than uncomplicated conjunctivitis	Refer to ophthalmologist; consider discontinuing
Osteonecrosis of the jaw, other sites	For ONJ, refer to dentist or dental surgeon; consider hold or discontinue
Severe musculoskeletal pain	Discontinue
Acquired Fanconi syndrome	Discontinue
Increased creatinine: <ol style="list-style-type: none"> 1. $\geq 44 \mu\text{mol/L}$ \uparrow if normal baseline** OR 2. $\geq 88 \mu\text{mol/L}$ \uparrow if abnormal at baseline OR 3. Serum creatinine $> 265 \mu\text{mol/L}$ ($> 400 \mu\text{mol/L}$ with TIH) 	Hold until recovered to within 10% of baseline (see table for dose adjustment for renal impairment at baseline)

**normal baseline creatinine is defined as $< 123 \mu\text{mol/L}$

Dosage with Hepatic Impairment:

There are no pharmacokinetic data in patients with impaired liver function. Zoledronic acid is not cleared by the liver; therefore, impaired liver function may not affect the pharmacokinetics of zoledronic acid.

Dosage with Renal Impairment:

			Starting Dose	
Creatinine		Creatinine Clearance (mL/min)	TIH	Other patients
		> 60	4 mg	4 mg
		50 - 60	4 mg	3.5 mg
		40 - 49	4 mg	3.3 mg
		30 - 39	Consider ↓	3 mg
> 265 µmol/L (> 400 µmol/L with TIH)	Or	<30	Do not treat	

Dosage in the elderly:

Similar efficacy and safety as compared to younger patients, but use with caution due to cardiac risks or renal function impairment.

Children:

Not recommended for use in children. Bone development was affected in growing animals.

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F - Administration Guidelines

- Do not infuse over a duration of less than 15 minutes.
- All patients should be adequately hydrated prior to and after administration of zoledronic acid, but overhydration should be avoided.

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- Mix with 100mL solution (D5W or NS) and infuse over \geq 15 minutes.
 - Do not mix with calcium or other divalent cation-containing solutions.
 - Compatible with PVC, glass, polyethylene and polypropylene containers or infusion lines.
 - Should be administered as a single intravenous solution in a line separate from all other drugs.
 - Store unopened vials at room temperature.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components, or other bisphosphonates
- Patients with non-corrected hypocalcemia at time of infusion or severe renal failure
- Zoledronic acid should not be given together with other bisphosphonates since the combined effects of these agents are unknown.
- Patients being treated with Aclasta® should not receive Zometa® concomitantly since they both contain zoledronic acid.
- Use of zoledronic acid in patients with severe renal impairment is not recommended.

Other Warnings/Precautions:

- The use of zoledronic acid with other nephrotoxins (cisplatin, NSAIDS, aminoglycosides, etc.), doses $>$ 4mg, infusion duration $<$ 15 minutes and previous bisphosphonate use are associated with an increased risk of renal failure.
- Use with extreme caution in combination with nephrotoxic agents or with agents which are renally excreted.
- Use with caution in patients with cardiac failure, especially in the elderly.
- Use with caution in patients with risk factors for ONJ, including patients receiving concomitant chemotherapy or anti-angiogenic agents; patients should be advised to avoid invasive dental procedures while receiving zoledronic acid.
- Caution in patients who have had thyroid surgery since they are susceptible to hypocalcemia due to relative hypoparathyroidism.
- The risk of hypocalcemia is increased in patients receiving loop diuretics, calcitonin or aminoglycosides.

Other Drug Properties:

- Carcinogenicity: Unlikely

Pregnancy and Lactation:

- Teratogenicity: Yes
Zoledronic acid is contraindicated for use in pregnancy. Animal studies suggest zoledronic

acid may cause fetal harm in pregnant women. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.

- Excretion into breast milk: Probable
Breastfeeding is contraindicated.
- Fertility effects: Documented in animals

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that can cause hypocalcemia (aminoglycosides, loop diuretics, calcitonin, esp in TIH)	↑ hypocalcemic effect	Additive effect	Caution (monitor calcium and magnesium levels)
Nephrotoxic drugs or drugs that can significantly impact renal function (e.g. selected antineoplastics, NSAIDs, ASA, ACE inhibitors, etc.)	↑ risk of renal dysfunction	Additive effects	Extreme Caution; monitor renal function
Aspirin	↑ incidence bronchospasm (theoretical)	Unknown	Avoid use in ASA sensitive patients
Anti-angiogenic drugs (e.g. sunitinib, bevacizumab)	↑ risk of ONJ	Additive	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
Renal function tests (serum creatinine and BUN)	Baseline, before each dose and during therapy, as indicated
Comprehensive dental evaluation of both hard and soft tissues; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment	Baseline (before starting treatment) and regular check-ups
Calcium, corrected levels (including serum albumin), electrolytes (including phosphate, magnesium)	baseline, before each dose and during therapy, as indicated
CBC	Baseline and regular
Clinical toxicity assessment for flu-like syndrome, dental, musculoskeletal, signs of acquired Fanconi syndrome, and ocular symptoms	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Ophthalmology examination	As indicated, with ocular symptoms

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J - Supplementary Public Funding**Exceptional Access Program ([EAP Website](#))**

- zoledronic acid - Treatment of bony metastases in hormone refractory prostate cancer (in those receiving outpatient care who do not meet the criteria of Cancer Care Ontario (CCO)), according to clinical criteria
- zoledronic acid - For the prevention of skeletal related events, in patients who have not experienced previous skeletal related events and who have bony metastases secondary to solid tumours, according to clinical criteria
- zoledronic acid - For the prevention of skeletal related events, in patients who have not experienced previous skeletal related events and who have bony metastases secondary to breast cancer or multiple myeloma, who are intolerant to pamidronate, according to clinical criteria
- zoledronic acid - For the treatment of patients with symptoms due to bony metastases

secondary to breast cancer or multiple myeloma who have failed or are intolerant to pamidronate, according to clinical criteria

- zoledronic acid - For the treatment of patient with symptoms due to bony metastases secondary to solid tumours (neither breast cancer nor multiple myeloma), considered on a case-by-case basis

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K - References

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

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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):1047-1053.

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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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