DRUG NAME: Zoledronic acid

SYNONYM(S): CGP-42446[1]

COMMON TRADE NAME(S): ZOMETA®

CLASSIFICATION: bone metabolism regulator

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

MECHANISM OF ACTION:

Zoledronic acid is a third generation, nitrogen containing bisphosphonate that inhibits bone resorption. It binds to hydroxyapatite crystals of the bone where it accumulates and is stored as an inactive drug. Zoledronic acid can persist for years in mineralized bone until it is released into systemic circulation once bone resorption occurs.[2,3] When ingested by osteoclasts, it inhibits osteoclastic formation, recruitment, activity, and induces osteoclast apoptosis.[1,4] In preclinical models, zoledronic acid prevents tumour adhesion to the bone, induces tumour cell apoptosis, and inhibits angiogenesis.[5] Zoledronic acid is structurally similar to pamidronate, but is 100-850 times more potent and is associated with higher binding affinity to bone and higher antiresorptive potential.[1,5-7]

PHARMACOKINETICS:

Distribution	low affinity for the cellular components of human blood; binds to bone	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding[6,8]	23-55%
Metabolism	does not undergo metabolism	
	active metabolite(s)	no
	inactive metabolite(s)	no
Excretion	eliminated intact via the kidney	
	urine	39%
	feces	< 3%
	terminal half life	146 hours
	clearance	3.7 L/h
Ethnicity	Japanese females had substantially higher systemic exposure than North Americans in a single-dose pharmacokinetic study (47% higher AUC and 39% higher C_{max}); exposure in Japanese males was comparable to the North American population	

Adapted from standard reference[6] unless specified otherwise.

USES:

Primary uses:
*Hypercalcemia of malignancy
*Bone metastases of solid tumours
*Multiple myeloma

Other uses:
Breast cancer[9,10]
Prevention of bone loss[11,12]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- do NOT use in patients who have a history of ***hypersensitivity reaction*** to zoledronic acid or other bisphosphonates[6]

Caution:
- ***osteonecrosis of the jaw (ONJ)*** has been reported with zoledronic acid; patients receiving anti-angiogenic drugs may be at higher risk[13-16]
- correct preexisting ***hypocalcemia*** prior to treatment and ensure adequate calcium and vitamin D intake[8]
- ZOMETA® contains the ***same active ingredient*** as ACLASTA® but they are ***NOT interchangeable***; formulations differ in concentration, dose, and indication[6]

Special populations: Safety in children has not been established. In animal studies, an increased incidence of primary spongiosa was reported in the long bones of growing animals.[6]

Carcinogenicity: No evidence of carcinogenic potential in animal studies.[6]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test; not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[6]

Fertility: Animal studies demonstrated reduced fertility, including increased pre- and post-implantation losses and a decreased number of live fetuses at doses lower than the equivalent human systemic exposure.[6]

Pregnancy: The potential risk to humans is unknown; however in animal studies, zoledronic acid crossed the placental barrier, was taken up into the developing fetal skeleton, and caused external, visceral, and skeletal malformations. In addition, increased maternal mortality was observed, possibly related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. As zoledronic acid is incorporated into the bone matrix and is gradually released over weeks to years, the amount of time required to reduce the risk of fetal harm after cessation of therapy is unknown. Zoledronic acid is not recommended during pregnancy.[4,6,13]

Breastfeeding is not recommended due to the potential secretion into breast milk. Animal studies have shown that other bisphosphonates are detected in the milk of lactating animals. Because zoledronic acid is released from the bone over weeks to years, there may be an ongoing risk to infants born post bisphosphonate therapy.[4,6]

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.[17,18] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[19,20]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (33%)
cardiac	arrhythmia (<1%)
	atrial fibrillation (<1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
eye	conjunctivitis, uveitis, episcleritis, scleritis, orbital inflammation (<1%)
gastrointestinal	*emetogenic potential:* rare[17,21,22]
	constipation (27%)[13]
	diarrhea (24%)
	nausea (6-12%)[23]
	stomatitis (8%)[13]
	vomiting (2%)[24]
general disorders and administration site conditions	*extravasation hazard:* none[25]
	fatigue (39%)
	pyrexia (32-44%)[6,13]; see paragraph following **Side Effects** table
	rigors (11%)[13]
immune system	hypersensitivity reaction (<1%)[13]
injury and poisoning	***atypical bone fracture*** (<1%); see paragraph following **Side Effects** table
investigations	***creatinine increase*** (severe 2%)
metabolism and nutrition	***hypocalcemia*** (5%); see paragraph following **Side Effects** table
	hypokalemia (10%)
	hypomagnesemia (11%)[13]
	hypophosphatemia (13%)[13]
musculoskeletal and connective tissue (see paragraph following **Side Effects** table)	arthralgia (21%)
	back pain (15%)
	bone pain (<1%)
	myalgia (23%)
	osteonecrosis of the jaw (1% during first year of treatment, 4% cumulative incidence)[26,27]
nervous system	headache (19%)
	dizziness (18%)
	paresthesia (15%)
psychiatric	agitation (13%)[13]
	anxiety (14%)[13]
	depression (14%)
	insomnia (15%)[13]
renal and urinary	***renal impairment*** (10-17%); see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (22%)
	interstitial lung disease (<1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
skin and subcutaneous tissue	rash, pruritis (<1%)
vascular	hypotension (1-11%)[6,13]

Adapted from standard reference[6] unless specified otherwise.

Atypical bone fractures (subtrochanteric and diaphyseal femur) are reported rarely in patients on long-term bisphosphonate therapy. These fractures often occur with minimal or no trauma and are slow to heal. Patients may experience prodromal pain for weeks or months before a fracture occurs and imaging often reveals stress fractures weeks to months prior to patients presenting with a completed femoral fracture. Assess both limbs in patients who present with thigh or groin pain because femoral fractures are often bilateral. Discontinue therapy if a femoral shaft fracture is confirmed.[4,8]

Flu-like symptoms caused by an acute phase reaction commonly occur within one to three days after administration of zoledronic acid, especially during the first few infusions. ***Pyrexia*** is the most common symptom, but myalgia, arthralgia, arthritis, swollen joints, and/or headache may also occur. There are no criteria to identify patients at risk, so routine prophylaxis is not recommended. Acetaminophen and oral fluids may help reduce flu-like symptoms if they occur. The symptoms are usually self-limiting, resolving within a few days to a few weeks.[4,6,13,22]

Severe, ***incapacitating bone, joint,*** and/or ***muscle pain*** has occurred within days to months of starting therapy. This severe pain is a syndrome distinct from the acute phase reaction. For some patients the pain is so severe they are unable to continue their normal activities of daily living and may require aids for walking. There are no known risk factors for this debilitating pain. Most patients have relief of symptoms after stopping drug therapy; however some patients report slow or incomplete pain resolution. Temporary or permanent discontinuation of the drug may be required as symptoms have reoccurred in a subset of patients rechallenged with zoledronic acid or another bisphosphonate.[6]

Hypocalcemia is reported and has been life-threatening in some cases. Neurologic adverse events (e.g., tonic-clonic seizures, tetany, and numbness) as well as QTc prolongation and cardiac arrhythmias secondary to severe hypocalcemia may occur. Onset of secondary effects may occur as soon as one day to several months after initiation of therapy. People who have calcium and mineral metabolism disturbances (e.g., hypoparathyroidism, thyroid/parathyroid surgery) may be particularly susceptible to developing hypocalcemia. Measure albumin-corrected serum calcium before treatment and correct calcium levels before administering zoledronic acid. Consider calcium and vitamin D supplementation during therapy. Symptoms of muscle spasms, numbness, and/or tingling, especially around the mouth should be promptly reported.[4,6,8]

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.[6] ONJ is more commonly observed with increasing bisphosphonate potency, dose intensity, and duration of treatment, particularly when treatment exceeds four years.[26-28] The risk of ONJ is higher with intravenous than with oral bisphosphonate treatment.[29,30] Multiple risk factors may play a role, including invasive dental procedures and pre-existing dental disease,[27,31] concomitant therapy with angiogenesis inhibitors, corticosteroids, and radiation to the head and neck[26,27,29,30], as well as certain comorbid medical conditions (e.g., anemia[29,31], cancer[26,30], coagulopathies[29], and diabetes[26,32]). For further details and management of ONJ, refer to *Bisphosphonates and Osteonecrosis of the Jaw in* ***Oral & Dental Care: Osteonecrosis of the Jaw.***

Renal toxicity resulting in renal failure, dialysis, and/or death has been reported in patients with both normal and impaired renal function. Because zoledronic acid is excreted exclusively by the kidney, the risk of adverse reactions may be greater in patients with pre-existing renal impairment. Other risk factors include; dehydration, advanced age, concomitant nephrotoxic drugs or drugs that significantly impact renal function, prior bisphosphonate use, and/or

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multiple bisphosphonate cycles. To avoid inducing renal toxicity, zoledronic acid dose should not exceed 4 mg and the duration of infusion should be no less than 15 minutes. Assess renal function prior to and during therapy and withhold zoledronic acid for renal deterioration. If appropriate, zoledronic acid may be resumed at the same dose used prior to dose interruption if renal function returns to within 10% of baseline. Rarely, serious cases of acquired ***Fanconi syndrome*** have been reported. Symptoms include hyperaminoaciduria, glucosuria in the presence of normal serum glucose, and phosphaturia. Discontinue zoledronic acid in the setting of Fanconi syndrome.[4,8]

INTERACTIONS: No documented interactions reported.[6]

SUPPLY AND STORAGE:

Injection:
Novartis Pharmaceuticals Canada Inc. supplies zoledronic acid as 4 mg single-use (preservative-free) vials in a concentration of 0.8 mg/mL. Store at room temperature.[6]

Dr. Reddy's Laboratories Limited (distributed by Innomar Strategies Inc.) supplies zoledronic acid as 4 mg single-use (preservative-free) vials in a concentration of 0.8 mg/mL. Store at room temperature.[33]

Sandoz Canada Inc. supplies zoledronic acid as 4 mg single-use (preservative-free) vials in a concentration of 0.8 mg/mL. Store at room temperature.[34]

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: Do NOT reconstitute or dilute with calcium-containing solutions (e.g., lactated Ringer's solution) or other divalent cation-containing infusion solutions.[13]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	Do NOT use
Intermittent infusion[6]	***over at least 15 minutes***
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Dosage may be reduced, delayed or discontinued.

Adults:

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

Intravenous:

Cycle Length:

3-4 weeks[6]: 4 mg (range 3-4 mg) IV for one dose on day 1
(total dose per cycle 4 mg [range 3-4 mg])

12 weeks[35-37]: ***4 mg*** (range 3-4 mg) ***IV for one dose on day 1***
(total dose per cycle 4 mg [range 3-4 mg])

6 months[9,38,39]: ***4 mg IV for one dose on day 1***
(total dose per cycle 4 mg)

Concurrent radiation: no information found

Dosage in renal failure[6]*:* suggested dose modification:

Creatinine clearance (mL/min)	Dose
>60	4 mg
50-60	3.5 mg
40-49	3.3 mg
30-39	3 mg
<30	not recommended

$$\text{Calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$$

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

for hypercalcemia of malignancy[8]:

- mild to moderate impairment: no dose adjustment
- severe impairment (serum creatinine > 400 µmol/L): no information

Dosage in hepatic failure: no information found

Dosage in dialysis: no information found

Children: not indicated for use in children[6,13]

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