Regimen Monograph

A - Regimen Name

ZOLE Regimen

Zoledronic Acid

Disease Site	Gastrointestinal - Anus Gastrointestinal - Colorectal Gastrointestinal - Esophagus Gastrointestinal - Gastric / Stomach Gastrointestinal - Gastrointestinal Stromal Tumours Gastrointestinal - Hepatobiliary / Liver / Bile Duct Gastrointestinal - Neuroendocrine (GI) Gastrointestinal - Pancreas Gastrointestinal - Small bowel and appendix Sarcoma - GIST
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

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B - Drug Regimen

zoledronic acid	4 mg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Other Supportive Care:

- Patients with hypercalcemia should be adequately hydrated.
- Calcium and Vitamin D supplements should be considered in patients who have normal calcium levels with no history of hypercalcemia.
- (See Zoledronic Acid Monograph)

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered. Hypocalcemia must be corrected before administering zoledronic acid.

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

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: 1. ≥ 44 µmol/L ↑ if normal baseline** OR 2. ≥ 88 µmol/L ↑ if abnormal at baseline OR 3. Serum creatinine > 265 µmol/L (> 400 µmol/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 µmol/L

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.

Renal Impairment

			Starting Dose
Creatinine		**Creatinine Clearance (mL/min)**	**For Osteolytic Lesions**
		> 60	4 mg
		50 - 60	3.5 mg
		40 - 49	3.3 mg
		30 - 39	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.

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F - Adverse Effects

Refer to zoledronic acid drug monograph(s) for additional details of adverse effects

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Nausea, vomiting • Fatigue, flu-like symptoms • Cough, dyspnea (may be severe)	• Diarrhea • Musculoskeletal pain (may be severe) • Edema • Headache • Dizziness • Nephrotoxicity (may be severe) • Weight loss • Paresthesia • Depression • Abnormal electrolytes • Conjunctivitis	• Atypical fractures of the femur • Atrial fibrillation, arrhythmia • Osteonecrosis of the jaw (ONJ) or other sites • Hypersensitivity • Eye disorders • Acquired Fanconi syndrome

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G - Interactions

Refer to zoledronic acid drug monograph(s) for additional details

- Caution and monitor with drugs that cause hypocalcemia (e.g. aminoglycosides, loop diuretics, calcitonin)
- Caution and monitor with drugs that cause renal dysfunction (e.g. NSAIDs, ACE inhibitors)
- Avoid in patients with hypersensitivity to ASA given possible increased risk of bronchospasm (theoretical)
- Caution with antiangiogenic drugs (e.g. sunitinib, bevacizumab) given increased risk of ONJ

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H - Drug Administration and Special Precautions

Refer to zoledronic acid drug monograph(s) for additional details

Administration:

- 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.
- Mix with 100 mL solution (D5W or NS) and infuse over ≥ 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.

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

Other Warnings/Precautions:

- The use of zoledronic acid with other nephrotoxins, doses > 4mg, infusion duration < 15 minutes and previous bisphosphonate use are associated with an increased risk of renal failure.
- 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 hypocalcaemia due to relative hypoparathyroidism.

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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

- Renal function tests (serum creatinine and BUN); baseline, before each dose and during therapy, as indicated
- Calcium, corrected levels (including serum albumin), electrolytes (including phosphate, magnesium); baseline, before each dose and during therapy, as indicated
- CBC; baseline and as clinically indicated
- Comprehensive dental evaluation of both hard and soft tissues before starting bisphosphonate treatment; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment; regular check-ups
- Clinical toxicity assessment for flu-like syndrome, dental, signs of acquired Fanconi syndrome, musculoskeletal and ocular symptoms; at each visit

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

Suggested Clinical Monitoring

- Ophthalmology examination with ocular symptoms; as clinically indicated

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	16 minutes
Nursing Workload (average time per visit)	35 minutes

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K - References

Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial--the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. J Clin Oncol. 2003 Aug 15;21(16):3150-7.

Zoledronic acid drug monograph, Cancer Care Ontario.

January 2018 aligned disease site to ST-QBP

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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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