Regimen Monograph

A - Regimen Name

ZOLE(HYPER CA) Regimen

Zoledronic acid

Disease Site	Breast Central Nervous System Endocrine Gastrointestinal Genitourinary Gynecologic Head and Neck Hematologic Lung Sarcoma Skin Unknown Primary
Intent	Supportive Care 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.
Rationale and Uses	Treatment of tumour-induced hypercalcemia (corrected serum calcium ≥ 3 mmol/L) following adequate saline rehydration.

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B - Drug Regimen

zoledronic acid	4 mg	IV	Day 1

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C - Cycle Frequency

Single dose. Allow a minimum of 7 days prior to retreatment.

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D - Premedication and Supportive Measures

Other Supportive Care:

All patients should be adequately hydrated.

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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.

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

Dosage with toxicity

Dosage in myelosuppression: No dosage adjustment required

Non-hematologic 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: > 400 µmol/L with tumour-induced hypercalcemia	Hold until recovered to within 10% of baseline* (see table below 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

Renal function			**Zoledronic acid dose (mg)**
Creatinine		**Creatinine Clearance (mL/min)**	
> 400 µmol/L with tumour-induced hypercalcemia	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 - 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
- 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 100mL 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

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 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; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment; regular check-ups
- 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

- 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

Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19(2):558.

Zoledronic acid drug monograph, Cancer Care Ontario.

January 2018 ST-QBP regimen; new addition to Drug Formulary website

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M - Disclaimer

Regimen Abstracts

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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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