**Regimen Monograph**



## A - Regimen Name

# DENO Regimen

**Denosumab**

| | |
|---|---|
| **Disease Site** | Sarcoma - Giant Cell Tumour |
| **Intent** | Curative |
| **Regimen Category** | **Evidence-Informed :**<br><br>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 adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity. |

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## B - Drug Regimen

| | | | |
|---|---|---|---|
| **denosumab** | 120 mg | Subcut loading dose | Days 1, 8 and 15 (month 1) |

**(This drug is not currently publicly funded for this regimen and intent)**

**THEN,**

| | | | |
|---|---|---|---|
| **denosumab** | 120 mg | Subcut | Day 1 (starting month 2) |

**(This drug is not currently publicly funded for this regimen and intent)**

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## C - Cycle Frequency

**REPEAT EVERY 28 DAYS**

Until disease progression or unacceptable toxicity

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## D - Premedication and Supportive Measures

**Other Supportive Care:**

All patients, except those with hypercalcemia, should receive the following supplementation:

- at least 500mg of calcium daily
- at least 400 IU of vitamin D daily

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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.

Pre-existing hypocalcemia must be corrected prior to starting treatment. Patients being treated with denosumab should not be treated concomitantly with bisphosphonates.

## Dosage with toxicity

| Toxicity | Action |
|---|---|
| Grade 3 or 4 drug-related toxicity | Consider holding or discontinuing |
| Osteonecrosis of the jaw | Follow guidelines for management. Consider holding or discontinuing treatment. Refer patient to dentist or oral surgeon. |
| Hypocalcemia | Treat appropriately. Consider holding or discontinuing treatment if severe. |
| Anaphylaxis or significant hypersensitivity | Treat appropriately. Discontinue denosumab permanently. |

## Hepatic Impairment

No studies have been conducted in patients with hepatic impairment.

## Renal Impairment

No dose adjustment is required with renal impairment. Patients with renal impairment are at increased risk of severe life threatening hypocalcemia and require increased monitoring (refer to monitoring section).

## Dosage in the Elderly

No adjustment required. No overall differences in safety and efficacy.

## Dosage in Pediatrics

May impair bone growth and tooth eruption in pediatric patients. Safety and efficacy have not been established and therefore not indicated in pediatric patients, except in skeletally mature adolescents (aged 13-17 years) with giant cell tumour of bone. Severe hypercalcemia has been reported in patients with growing skeletons, weeks to months following denosumab discontinuation

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## F - Adverse Effects

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

| Common (25-49%) | Less common (10-24%) | Uncommon (< 10%),<br><br>but may be severe or life-threatening |
|---|---|---|
| • Nausea and vomiting<br>• Fatigue<br>• Anemia<br>• Musculoskeletal pain | • Anorexia, weight loss<br>• Constipation<br>• Diarrhea<br>• Abdominal pain<br>• Cough, dyspnea (may be severe)<br>• ↓ PO4, ↓ Ca (may be severe)<br>• Headache<br>• Fever | • Arterial thromboembolism<br>• Venous thromboembolism<br>• Renal failure<br>• Arrhythmia, cardiotoxicity<br>• Bone fracture (including atypical femoral; multiple vertebral after treatment discontinuation)<br>• Osteonecrosis of the jaw<br>• ↑ LFTs (may be severe)<br>• Secondary malignancies<br>• Hypersensitivity |

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## G - Interactions

Refer to denosumab drug monograph(s) for additional details

No formal drug-drug interaction studies have been documented. Caution with drugs that may cause hypocalcemia.

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## H - Drug Administration and Special Precautions

Refer to denosumab, denosumab drug monograph(s) for additional details

**Administration:**

- Inject subcutaneously in the upper arm, upper thigh, or the abdomen.
- Should not be administered intravenously, intramuscularly or intradermally
- Use a 27-gauge needle to withdraw or inject the drug. Avoid vigorous shaking of the drug.
- Denosumab should appear clear, colourless to slightly yellow. It may contain trace amounts of translucent or white proteinaceous particles. Do not use if the solution is discoloured, cloudy, contains many particles or foreign matter.
- If a dose is missed, it may be given as soon as possible and the subsequent injection should be scheduled q4 weeks from the most recent injection date.
- Keep refrigerated in the original carton between 2-8°C. Protect from direct light
- Before use, the drug vial (in its original container) can be brought to room temperature (usually takes 15-30 minutes). Do not warm the drug by other methods. Once removed from the refrigerator, it must be stored at room temperature (≤ 25°C) and used within 30 days.

**Contraindications:**

- Patients who have a hypersensitivity to this drug or any of its components
- Do not use Xgeva® with Prolia®, as both products contain the same active ingredient, denosumab.

**Precautions:**

- Pre-existing hypocalcemia must be corrected before starting denosumab treatment. Risk of hypocalcemia is greater in patients with moderate to severe renal impairment. Patients, except those with hypercalcemia, should receive adequate calcium and vitamin D supplementation.
- Patients being treated with denosumab should not be treated concomitantly with bisphosphonates
- Risk-benefit should be assessed for patients with risk factors for ONJ before starting treatment.
- Denosumab is not recommended for use in pregnancy and lactation; impaired bone or teeth development have been observed in young animals. Adequate contraception should be used by both sexes during treatment, at for at least 5 months after the last denosumab dose.
- Women who become pregnant or breastfeed during denosumab treatment are encouraged to enroll in the manufacturer's Pregnancy Surveillance Program or Lactation Surveillance Program, respectively.

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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

- Calcium, phosphate, magnesium - If no hypercalcemia: baseline, within 2 weeks of the first dose, and as clinically indicated. In hypercalcemia: baseline, before each dose and as clinically indicated. Additional monitoring with renal dysfunction, symptoms of hypercalcemia and in patients with growing skeleton.
- Dental examination with appropriate preventative dentistry should be considered prior to treatment. Regular dental check-ups. Avoid invasive dental surgeries while on treatment.
- Vertebral fractures; evaluate patient risk after treatment discontinuation
- Clinical toxicity assessment for fatigue, musculoskeletal effects, hypocalcemia, ONJ, cough/dyspnea; at each visit

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

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## J - Administrative Information

Refer to local administration guidelines.

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| Approximate Patient Visit | 15 minutes |
| Pharmacy Workload (average time per visit) | 13.85 minutes |
| Nursing Workload (average time per visit) | 25.833 minutes |

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## K - References

Denosumab drug monograph, Cancer Care Ontario.

Chawla S, Henshaw R, Seeger L, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol 2013;14(9):901-8.

Ueda T, Morioka H, Nishida Y, et al. Objective tumor response to denosumab in patients with giant

cell tumor of bone: a multicenter phase II trial. Ann Oncol 2015;26(10):2149-54.

**PEBC Advice Documents or Guidelines**

- Systemic therapy of denosumab in altering surgical outcomes in patients with giant cell tumour of bone

**March 2021** Added PEBC guideline link

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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.*

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***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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