Regimen Monograph

A - Regimen Name

DENO Regimen

Denosumab

Disease Site	Genitourinary - Prostate
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.
Rationale and Uses	To reduce the risk of developing skeletal-related events in patients with bone metastases from prostate cancer (Health Canada indication); funded for patients with castrate resistant prostate cancer (prior castration or castrate serum testosterone levels [<1.7 nmol/L or <50ng/dL]) and elevated PSA or progressive bony disease
Supplementary Public Funding	**denosumab** New Drug Funding Program (Denosumab - Hormone Refractory Prostate Cancer) (Denosumab is considered through the New Drug Funding Program for those receiving prostate cancer treatment from a cancer clinic.) **denosumab** Exceptional Access Program (denosumab - Bony metastases in hormone refractory prostate cancer, with specific criteria) (EAP Website)

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B - Drug Regimen

denosumab	120 mg	SC	Every 4 weeks

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Unless unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Not applicable

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.

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

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G - Interactions

Refer to denosumab drug monograph(s) for additional details

- Exercise caution when given with drugs that may cause hypocalcemia. Monitor calcium levels closely.

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H - Drug Administration and Special Precautions

Refer to 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:

- Contraindicated in 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:

- Patients being treated with denosumab should not be treated concomitantly with bisphosphonates
- 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 (see Dosing section).
- Risk-benefit should be assessed for patients with risk factors for ONJ before starting treatment.
- Adequate contraception should be used by both sexes during treatment, at for at least 5 months after the last denosumab dose.
- Fertility effects: Unlikely

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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 - 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.

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.

Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813–22.

PEBC Advice Documents or Guidelines

- Bone Health and Bone-Targeted Therapies for Prostate Cancer

July 2018 Updated adverse effects and monitoring sections

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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