Drug Monograph

A - Drug Name

denosumab

COMMON TRADE NAME(S): Xgeva®; Wyost™

- Different denosumab products are **not interchangeable**.
- For additional information on biosimilars, refer to:
  - Position Statements for the Clinical Operational Implementation of Oncology Biosimilars from the pan-Canadian Clinical Operations Working Group
  - Clinician Fact Sheet

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B - Mechanism of Action and Pharmacokinetics

Denosumab is a fully human IgG2 monoclonal antibody, which targets the human receptor activator of nuclear factor kappa-B ligand (RANKL). Denosumab inhibits osteoclast formation, function, survival, and thus reduces bone resorption.

Absorption	Drug exposure is approximately dose-proportional for doses of 60mg or higher. Steady state is reached on or after 6 doses of 120mg q4 weeks. Pharmacokinetics do not change with age, weight, race, time or multiple dosing. Bioavailability SC: 62%
Distribution	Volume of distribution and clearance were observed to be proportional to body weight.

Metabolism	Likely via immunoglobulin clearance pathways and not metabolized or eliminated hepatically	
Elimination	Clearance is believed to occur via the reticuloendothelial system.	
	Urine	Not likely
	Feces	Not likely
	Half-life	28 days (mean half-life, 120mg q4 week dosing)

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C - Indications and Status

Health Canada Approvals:

- For reducing the risk of developing skeletal-related events in patients with multiple myeloma and in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours
- For the treatment of hypercalcemia of malignancy refractory to intravenous bisphosphonate
- For the treatment of adults and skeletally mature adolescents with giant cell tumour of bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: None

The following side effects are listed irrespective of causality from randomized controlled trials of 120 mg in cancer patients with bone metastases, usually in combination with systemic anticancer therapy.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (2%)	E
	Arterial thromboembolism (<1%)	E
	Cardiotoxicity (2%)	D
	Hypertension (5%)	E
	Hypotension (3%)	E
	Venous thromboembolism (2%)	E
Dental	Pain (4%)	E
Dermatological	Hand-foot syndrome (4%)	E
	Nail disorder (2%)	E
	Rash (7%)	E
Gastrointestinal	Abdominal pain (10%)	E
	Anorexia, weight loss (23%)	E
	Constipation (21%)	E
	Diarrhea (20%)	E
	Dyspepsia (5%)	E
	Mucositis (5%)	E
	Nausea, vomiting (31%)	I
General	Fatigue (27%)	E
	Fever (14%)	I E
Hematological	Anemia (27%)	E
	Myelosuppression (10%)	E
Hepatobiliary	Hepatic failure (<1%)	D
	↑ LFTs (3%)	E
Hypersensitivity	Hypersensitivity (rare)	I
Infection	Infection (8%) (including cellulitis)	E
Metabolic /	Abnormal electrolyte(s) (5%) (not including calcium, PO4	E

Endocrine	changes)	
	↓ Ca (10%) (severe 3%)	E D
	↑ Ca (rarely severe, observed after treatment ends in patients with GCTB or growing skeletons)	E
	Hyperglycemia (4%)	E
	Hypoglycemia (1%)	E
	↓ PO4 (15%) (severe)	E
Musculoskeletal	Fracture (6%) (including atypical femoral fractures and multiple post-treatment vertebral fractures)	D
	Musculoskeletal pain (25%) (may be severe)	E
	Osteonecrosis of jaw (2%)	D
Neoplastic	Secondary malignancy (1%)	D L
Nervous System	Anxiety (7%)	E
	Cognitive disturbance (3%)	E
	Depression (7%)	E
	Dizziness (8%)	E
	Dysgeusia (4%)	E
	Headache (13%)	E
	Paresthesia (6%)	E
Ophthalmic	Eye disorders (2% - lacrimation, conjunctivitis, blurred vision)	E
Renal	Creatinine increased (4%)	E
	Renal failure (3%)	E
Respiratory	Cough, dyspnea (21%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for denosumab in bone metastases include nausea/vomiting, fatigue and hypophosphatemia.

Denosumab may cause severe **hypocalcemia** (fatal in rare cases). The risk is increased with renal impairment and may be accompanied by elevated parathyroid hormone levels. Patients (except those with hypercalcemia) should receive calcium, vitamin D and magnesium supplements (as indicated) while on denosumab treatment. (See Dosing section).

Worsening **hypercalcemia** has been reported when denosumab is used to treat hypercalcemia and has also been reported in patients with GCTB or growing skeletons, weeks to months following denosumab discontinuation.

Atypical fractures of the femur (subtrochanteric or diaphyseal) have been reported. They are often bilateral, occur with minimal or no trauma, with symptoms including thigh or groin pain. Imaging features of stress features may be seen weeks to months before presentation with a completed femoral fracture. These fractures have also been reported in patients with certain conditions such as vitamin D deficiency, rheumatoid arthritis, hypophosphatasia and with/without use of certain medications (e.g. antiresorptive therapy, glucocorticoids, proton pump inhibitors).

Multiple vertebral fractures following denosumab discontinuation were reported in post-marketing. These were not due to bone metastases and particularly occurred in patients with risk factors such as osteoporosis or prior fractures.

Binding antibodies to denosumab have been reported in < 1% of patients who had up to 3 years of treatment, but neutralizing antibodies have not been reported. The clinical relevance is limited.

A higher rate of **cellulitis** has been observed in patients on denosumab.

Osteonecrosis of the jaw (ONJ) is a common cause of denosumab discontinuation in clinical trials. The incidence of ONJ was observed to be higher with longer duration of exposure (1% with <12 months versus 4% in the second year, and 5% per year thereafter). Median onset in prostate or breast cancer patients was 20.6 months. Poor oral hygiene, invasive dental procedures, treatment with anti-angiogenic drugs, local gum or oral infection were risk factors for ONJ. Other risk factors include infections, older age, concomitant treatments (e.g., chemotherapy, corticosteroids, head and neck radiotherapy), smoking and previous bisphosphonate treatment. ONJ has also been reported after the end of treatment, with a majority of cases occurring 5 months after the last dose. Dental evaluation is recommended prior to starting treatment and during therapy, but invasive dental procedures should be avoided during treatment.

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E - Dosing

Note: Different denosumab products are **not interchangeable**.

Refer to protocol by which patient is being treated.

Pre-existing hypocalcemia must be corrected prior to starting treatment.

Patients being treated with denosumab should not be treated concomitantly with bisphosphonates or other denosumab products.

Adults:

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

Myeloma and bone metastases from cancer:

Subcutaneous: 120 mg every 4 weeks

Hypercalcemia of malignancy and Giant cell tumour of bone:

Subcutaneous: 120 mg Days 1, 8 and 15 of month 1 (loading dose), THEN

Subcutaneous: 120 mg every 4 weeks

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.

Dosage with Hepatic Impairment:

No studies have been conducted in patients with hepatic impairment.

Dosage with 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.

Children:

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 - Administration Guidelines

Note: Different denosumab products are **not interchangeable**.

- 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.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Hypocalcemia

Other Warnings/Precautions:

- Patients being treated with denosumab should not be treated concomitantly with bisphosphonates or other denosumab products.
- 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).
- A risk-benefit assessment should be performed for patients with risk factors for ONJ before starting treatment.
- Dental examination with appropriate preventative dentistry should be considered prior to treatment. Invasive dental surgeries should be avoided while on treatment.

Other Drug Properties:

- Carcinogenicity: No
- Immunosuppressive: No

Pregnancy and Lactation:

- Genotoxicity: Unlikely
- Fetotoxicity: Yes
- Pregnancy:
  Denosumab is not recommended for use in pregnancy Impaired bone or teeth development have been observed in young animals. Adequate contraception should be used by both patients and their partners during treatment, and for at least **5 months** after the last dose.
- Excretion into breast milk: Unknown
  Although it is unknown whether denosumab excretes into breast milk, mammary gland development and lactation were impaired in animals lacking RANKL.
- Breastfeeding:
  Denosumab is not recommended for use in breastfeeding.
- Fertility effects: Unlikely

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H - Interactions

No formal drug-drug interaction studies have been documented.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that may cause hypocalcemia (e.g. anticonvulsants - phenytoin, phenobarbital; foscarnet)	↑ risk of hypocalcemia	Additive	Caution; monitor calcium levels closely

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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

Monitor Type	Monitor Frequency
Calcium, phosphate, magnesium	No hypercalcemia: baseline, within 2 weeks of the first dose, and as clinically indicated. In patients with hypercalcemia: baseline, before each dose and as clinically indicated. Additional monitoring with renal dysfunction, symptoms of hypercalcemia / hypocalcemia, and after denosumab discontinuation especially in patients with growing skeletons.
Oral / Dental examination	Baseline and regular
Clinical toxicity assessment for fatigue, musculoskeletal effects, hypocalcemia, ONJ, hypersensitivity, cellulitis, cough/dyspnea	At each visit
Vertebral fractures	Evaluate patient's risk after treatment discontinuation

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

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Denosumab (Biosimilar) - Hormone Refractory Prostate Cancer

ODB Limited Use (ODB Formulary)

- denosumab (Wyost brand) - For the treatment of bony metastases for patients with hormone refractory prostate cancer as determined by an elevated PSA level, or evidence of progressive bony disease, despite castrate serum testosterone levels or having undergone orchidectomy, according to clinical criteria

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K - References

McEvoy GK, editor. AHFS Drug Information 2011. Bethesda, Maryland: American Society of Health-System Pharmacists; 2011. Denosumab; p. 2676-8, and Foscarnet; p. 873.

Muir VJ, Scott LJ. Denosumab: in cancer treatment-induced bone loss. BioDrugs 2010; 24(6): 379-86.

DILANTIN® (phenytoin) product monograph. Pfizer Canada Inc.; 29 July 2010.

PROLIA® (denosumab) prescribing information. Amgen Inc. (US); September 2011.

XGEVA® (denosumab) product monograph. Amgen Canada Inc.; April 2018 and May 2023.

XGEVA® (denosumab) prescribing information. Amgen Inc. (US); November 2010 and June 2020.

WYOST™ (denosumab) product monograph. Sandoz Canada Inc., March 1, 2024.

September 2024 Updated Supplementary Public Funding section; August 2024 - Updated NDFP form, added biosimilar information, aligned emetogenic potential with regimen monographs, updated Contraindications, Precautions, Pregnancy/lactation, and Monitoring sections

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L - Disclaimer

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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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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