DRUG NAME: Denosumab

SYNONYM(S):

COMMON TRADE NAME(S): XGEVA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Denosumab is a human monoclonal antibody that binds to the human RANK ligand (RANKL) on the surface of osteoclasts and their precursors. Denosumab prevents RANKL from binding to RANK, which inhibits osteoclast formation, function and survival, leading to decreased bone loss and destruction. Osteoclast activity is a key mediator of bone disease in metastatic tumours and multiple myeloma.[1,2]

PHARMACOKINETICS:

Distribution	bioavailability 62%; onset 3-7 days[2,3]; time to peak 10 days (range 3-21 days)[3]; steady state in 6 months[4,5]	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	no information found
Metabolism	degradation to peptides and amino acids in the circulation; hepatic metabolism is not involved[6]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	renal[7] or hepatic[6] elimination are not involved	
	urine	no information found
	feces	no information found
	terminal half life[2,3]	25 - 28 days
	clearance[2,8]	faster clearance at lower doses; not affected by weight change
Sex	no difference	
Elderly	no difference	
Ethnicity	no difference	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Prevention of skeletal-related events from bone metastases from solid tumours

*Giant-cell tumour of bone

*Hypercalcemia of malignancy

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- XGEVA® contains the ***same active ingredient*** as PROLIA®; they are ***NOT interchangeable***. Formulations differ in concentration, dosing, and indications.[2,9]
- ***Hypocalcemia*** may occur with denosumab; pre-existing hypocalcemia should be corrected prior to initiating treatment.[2]
- ***Osteonecrosis of the jaw*** (ONJ) has been reported. Patients who have had invasive dental procedures, poor oral hygiene or other periodontal disease may be at risk for ONJ. A dental examination and necessary preventive dentistry is recommended prior to initiating treatment with denosumab.[2]

Special populations: Denosumab is not recommended for use in pregnant women or in pediatric patients, with the exception of skeletally mature adolescents. Denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.[10]

Carcinogenicity: Secondary malignancies were reported in 1% of patients in a pooled safety analysis.[2]

Mutagenicity: No information found. Denosumab is made up of amino acids; therefore, it is unlikely to react with DNA or other chromosomal material.[2]

Fertility: Denosumab had no effect on female fertility or male reproductive organs in animal studies.[2]

Pregnancy: FDA Pregnancy Category D.[11] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situtation or for a serious disease for which safer drugs cannot be used or are ineffective).
In animal studies, denosumab exposure resulted in increased fetal loss, stillbirths, and postnatal mortality, as well as skeletal abnormalities, impaired bone resorption, reduced bone strength, bone fractures, reduced hematopoiesis, tooth malalignment, dental dysplasia, absent peripheral lymph nodes, and decreased neonatal growth in the infants.[10]

Breastfeeding is not recommended due to the potential secretion into breast milk. Pregnant animals also showed altered mammary gland maturation leading to impaired lactation postpartum.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[12,13]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (27%)
	febrile neutropenia (2%)
	leukopenia (6%)
	neutropenia (10%)
	thrombocytopenia (8%)
cardiac	atrial fibrillation (2%)
	cardiac failure (2%)
	tachycardia (3%)
eye	lacrimation, increased (2%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	vision, blurred (2%)
gastrointestinal	*emetogenic potential:* rare[14]
	abdominal pain (10%)
	ascites (2%)
	constipation (21%)
	diarrhea (20%)
	dry mouth (2%)
	dyspepsia (5%)
	dysphagia (2%)
	flatulence (2%)
	gastritis (2%)
	gastroesophageal reflux disease (2%)
	nausea (31%)
	stomatitis (5%)
	toothache (4%)
general disorders and administration site conditions	*extravasation hazard:* none[15]
	asthenia (21%)
	chest pain, non-cardiac (9%)
	edema peripheral (17%)
	fatigue (27%)[2]
	pain (8%)
	pyrexia (14%)
infections and infestations	cellulitis (2%); may lead to hospitalization
	herpes zoster (2%)
	oral candidiasis (3%)
	respiratory tract infection (1%)
	rhinitis (2%)
	sinusitis (3%)
	upper respiratory infection (4%)
	urinary tract infection (8%)
injury, poisoning, and procedural complications	contusion (2%)
	fall (2%)
	lumbar vertebral fracture (4%)
	rib fracture (6%)
	thoracic vertebral fracture (5%)
investigations	alkaline phosphatase increase (3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	ALT increase (1%); up to 5 X ULN
	AST increase (7%); up to 2.5 X ULN
	bilirubin, total increase (<1%); up to 10 X ULN[8]
	creatinine increase (4%)
	hemoglobin decrease (2%)
	weight loss (12%)
	weight gain (2%)
metabolism and nutrition	dehydration (6%)
	hypercholesterolemia (7%)[8]
	hyperglycemia (4%)
	hyperkalemia (2%)
	hypoalbuminemia (2%)
	hypocalcemia (10%, severe 3%); see paragraph following **Side Effects** table
	hypokalemia (5%)
	hypomagnesemia (2%)
	hyponatremia (2%)
	hypophosphatemia (32%, severe 15%)
musculoskeletal and connective tissue	arthralgia (20%)
	back pain (25%)
	bone pain (20%)
	muscle spasms (4%)
	muscular weakness (4%)
	musculoskeletal chest pain (7%)
	musculoskeletal pain (13%)
	myalgia (5%)
	neck pain (4%)
	osteonecrosis of the jaw (2%)[7,16]; see paragraph following **Side Effects** table
	pain in extremity (18%)
	pain in jaw (4%)
neoplasms	secondary malignancies (1%)
nervous system	dizziness (8%)
	dysesthesia (4%)
	dysgeusia (4%)
	headache (13%)
	lethargy (2%)
	paresthesia (6%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	peripheral neuropathy (3%)
	somnolence (2%)
	spinal cord compression (3%)
	syncope (2%)
psychiatric	anxiety (7%)
	confusional state (3%)
	depression (7%)
	insomnia (11%)
renal and urinary	cystitis (2%)
	dysuria (4%)
	hematuria (4%)
	hydronephrosis (2%)
	renal failure (3%)
	urinary retention (4%)
reproductive system and breast disorders	pelvic pain (3%)
respiratory, thoracic and mediastinal	cough (15%)
	dyspnea (21%)
	epistaxis (4%)
	hemoptysis (2%)
	oropharyngeal pain (3%)
	pleural effusion (5%)
	pulmonary embolism (2%)
	respiratory failure (3%)
skin and subcutaneous tissue	alopecia (9%)
	erythema (2%)
	hyperhidrosis (2%)
	palmar-plantar erythrodysesthesia (4%)
	pruritus (4%)
	rash (7%)
vascular	deep vein thrombosis (2%)
	hypertension (5%)
	hypotension (4%)

Adapted from standard reference[2] unless specified otherwise.

Hypocalcemia can occur with denosumab. Some fatalities have been reported.[17] Symptoms include: muscle spasms, twitches, cramps, and numbness or tingling in fingers, toes or around the mouth.[2] In severe cases, altered

mental status, tetany, seizures, and QTc prolongation have been reported.[17] The serum calcium nadir occurs approximately 10 days after the dose in patients with normal renal function.[18,19] The risk of hypocalcemia is greater in patients with a history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, small bowel surgery, severe renal impairment (creatinine clearance less than 30 mL/min) or on dialysis. Treatment related hypocalcemia may be prevented by supplementing with at least 500 mg calcium daily and 400 IU vitamin D daily.[2] Monitor for hypocalcemia and correct as necessary.[17]

Osteonecrosis of the jaw (ONJ) is a serious adverse event that may occur spontaneously. Symptoms include: jaw pain, osteomyelitis, osteitis, bone erosion, tooth/periodontal infection or gingival ulceration/erosion.[2,6,7] The median time to develop ONJ is 14 months.[6,20] Resolution occurs in 40% of patients.[2,7,9,20] ONJ has been associated with dental extraction and/or local infection with delayed healing. If invasive dental procedures are indicated, delay denosumab treatment until initial bone healing has occurred.[21] For further information on the prevention of ONJ during treatment with bone-modifying agents, refer to *Bisphosphonates and Osteonecrosis of the Jaw* in ***Oral & Dental Care: Osteonecrosis of the Jaw.***

INTERACTIONS: No information found.

SUPPLY AND STORAGE:

***Injection*:** Amgen Canada Inc. supplies denosumab as single-use vials containing 120 mg of denosumab in 1.7 mL preservative-free solution. Refrigerate. Protect from light.[2]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- Vials may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is cloudy or contains many particles.[2]
- Once removed from the refrigerator, intact vials may be stored at room temperature for up to 30 days.[2]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous[10,22,23]	***in the upper arm, upper thigh, or abdomen***
Intradermal[10]	do NOT use
Intramuscular[10]	do NOT use
Direct intravenous[10]	do NOT use
Intermittent infusion[10]	do NOT use
Continuous infusion[10]	do NOT use
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Subcutaneous	4 weeks[10,22]	***120 mg SC*** for one dose on day 1 (total dose per cycle 120 mg)
	4 weeks[10,23]	Cycle 1 (loading): 120 mg SC for one dose on days 1, 8 and 15 (total dose for cycle one 360 mg) Cycle 2 onwards (maintenance): 120 mg SC for one dose on day 1 (total dose per cycle 120 mg)

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure: no adjustment required[2]

Dosage in hepatic failure: no information found

Dosage in dialysis: no adjustment required[2]

***Children*:** not recommended in children, except skeletally mature adolescents[10]

REFERENCES:

1. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet Oncol 2010;11(3):275-280.
2. Amgen Canada Inc. XGEVA® product monograph. Mississauga, Ontario; 14 October 2011.
3. Basow DS editor. Denosumab. UpToDate 19.2 ed. Waltham, Massachusetts: UpToDate®; accessed 27 October 2011.
4. Drug Facts and Comparisons® (database on the Internet). Denosumab. Wolters Kluwer Health Inc. Facts and Comparisons® eAnswers, updated periodically. Available at: http://online.factsandcomparisons.com. Accessed 27 October 2011.
5. MICROMEDEX® 2.0 Drug Interactions (database on the Internet). Denosumab. Thomson Reuters MICROMEDEX® 2.0, updated periodically. Available at: http://www.micromedex.com. Accessed 27 October 2011.
6. Scott L, Muir VJ. Denosumab in the prevention of skeletal-related events in patients with bone metastases from solid tumours. Drugs 2011;71(8):1059-1069.
7. Stopeck AT, Lipton A, Body J, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010;28(35):5132-5139.
8. Amgen Canada Inc. PROLIA® product monograph. Mississauga, Ontario; 18 October 2011.
9. Elaine Yim Medical Information Manager. Personal communication. AMGEN Medical Information; 25 November 2011.
10. Amgen Canada Inc. XGEVA® product monograph. Mississauga, Ontario; 19 October 2015.
11. Amgen Inc. PROLIA® prescribing information. Thousand Oaks, California; March 2016.

12. Anna Tinker MD. Personal communication. BC Cancer Agency Genitourinary Tumour Group; 20 December 2011.
13. Victoria Kletas MSc Pharm. Personal communication. BC Cancer Agency Genitourinary Tumour Group; 28 Dec 2011.
14. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2011.
15. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 November 2010.
16. Van Poznak CH, Temin S, Yee GC, et al. American society of clinical oncology clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol 2011;29(9):1221-1227.
17. Amgen Canada Inc. Health Canada Endorsed Important Safety Information on XGEVA® (denosumab) - Risk of severe symptomatic hypocalcemia, including fatal cases. Health Canada, 28 May 2012. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/. Accessed 31 May 2012.
18. AHFS Drug Information® (database on the Internet). Denosumab. Lexi-Comp Inc., May 2011. Available at: http://online.lexi.com. Accessed 27 October 2011.
19. Amgen Inc. PROLIA® product monograph. Thousand Oaks, California; September 2011.
20. Aghaloo TL, Felsenfeld AL, Tetradis S. Osteonecrosis of the jaw in a patient on denosumab. J Oral Maxillofac Surg 2010;68:959-963.
21. Van Poznak CH, Temin S, Yee GC, et al. American society of clinical oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol 2011;29(9):1221-1227.
22. BC Cancer Agency. (SCDMAB) BCCA Protocol Summary for Treatment of Prostate Cancer Bone Metastases using Denosumab (XGEVA®). Vancouver, British Columbia: BC Cancer Agency; 1 May 2014.
23. BC Cancer Agency Sarcoma Tumour Group. (USANADENO) BCCA Protocol Summary for Denosumab for Neoadjuvant Use in Patients with Non-Metastatic Operable Giant Cell Tumour of the Bone. Vancouver, British Columbia: BC Cancer Agency; 1 Jul 2016.