Denosumab: Drug information

(For additional information see "Denosumab: Patient drug information" and see "Denosumab: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Prolia; Xgeva

Brand Names: Canada

Prolia; Xgeva

Pharmacologic Category

Bone-Modifying Agent; Monoclonal Antibody

Dosing: Adult

Note: Administer calcium and vitamin D as necessary to prevent or treat hypocalcemia

Hypercalcemia of malignancy (Xgeva): SubQ: 120 mg every 4 weeks; during the first month, give an additional 120 mg on days 8 and 15 (Hu 2014)

Prevention of skeletal-related events in bone metastases from solid tumors (Xgeva): SubQ: 120 mg every 4 weeks (Fizazi 2011; Henry 2011; Stopeck 2010)

Treatment of androgen deprivation-induced bone loss in men with prostate cancer (Prolia): SubQ: 60 mg as a single dose, once every 6 months (Smith 2009)

Treatment of aromatase inhibitor-induced bone loss in women with breast cancer (Prolia): SubQ: 60 mg as a single dose, once every 6 months (Ellis 2008)

Treatment of giant cell tumor of the bone (Xgeva): SubQ: 120 mg once every 4 weeks; during the first month, give an additional 120 mg on days 8 and 15 (Blay 2011; Thomas 2010)

Treatment of osteoporosis in men or postmenopausal women (Prolia): SubQ: 60 mg as a single dose, once every 6 months

Bone destruction caused by rheumatoid arthritis (off-label use): SubQ: 60 mg or 180 mg as a single one time dose and repeated at 6 months (in combination with continued methotrexate); a total of 2 doses was administered in the study (Cohen 2008). Additional data may be necessary to further define the role of denosumab in this condition.

Dosing: Pediatric

(For additional information see "Denosumab: Pediatric drug information")

Note: Administer calcium and vitamin D as necessary to prevent or treat hypocalcemia

Treatment of giant cell tumor of the bone (Xgeva): Adolescents (skeletally mature) 13 to 17 years: SubQ: 120 mg once every 4 weeks; during the first month, give an additional 120 mg on days 8 and 15

Dosing: Geriatric Refer to adult dosing.

Dosing: Renal Impairment Monitor patients with severe impairment (CrCl <30 mL/minute or on dialysis) closely due to increased risk of hypocalcemia.

Prolia: No dosage adjustment necessary.

Xgeva: There are no dosage adjustments provided in the manufacturer's labeling. Guidelines suggest dosage adjustment is not necessary; close monitoring for hypocalcemia is recommended (Gravalos 2016; Van Poznak 2011).

Dosing: Hepatic Impairment There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Subcutaneous [preservative free]:

Prolia: 60 mg/mL (1 mL) [contains mouse (murine) and/or hamster protein]

Xgeva: 120 mg/1.7 mL (1.7 mL)

Generic Equivalent Available (US) No

Medication Guide and/or Vaccine Information Statement (VIS) An FDA-approved patient medication guide, which is available with the product information and as follows, must be dispensed with this medication:

Prolia: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125320s181lbl.pdf#page=27

Administration SubQ: Denosumab is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally. Prior to administration, bring to room temperature in original container (allow to stand ~15 to 30 minutes); do not warm by any other method. Solution may contain trace amounts of translucent to white protein particles; do not use if cloudy, discolored (normal solution should be clear and colorless to pale yellow), or contains excessive particles or foreign matter. Avoid vigorous shaking. Administer via SubQ injection in the upper arm, upper thigh, or abdomen.

Prolia: If a dose is missed, administer as soon as possible, then continue dosing every 6 months from the date of the last injection.

Use

Hypercalcemia of malignancy (Xgeva): Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

Osteoporosis/bone loss (Prolia): Treatment of osteoporosis in postmenopausal women at high risk of fracture; treatment of osteoporosis (to increase bone mass) in men at high risk of fracture; treatment of bone loss in men receiving androgen-deprivation therapy (ADT) for nonmetastatic prostate cancer;

treatment of bone loss in women receiving aromatase inhibitor (AI) therapy for breast cancer

Tumors (Xgeva): Prevention of skeletal-related events (eg, fracture, spinal cord compression, bone pain requiring surgery/radiation therapy) in patients with bone metastases from solid tumors; treatment of giant cell tumor of the bone in adults and skeletally mature adolescents that is unresectable or where surgical resection is likely to result in severe morbidity

Limitation of use: Denosumab is NOT indicated for prevention of skeletal-related events in patients with multiple myeloma

Use: Off-Label

Bone destruction caused by rheumatoid arthritis

Medication Safety Issues

Sound-alike/look-alike issues:

Denosumab may be confused with daratumumab, dinutuximab

Xgeva may be confused with Jevtana, Xofigo, Xtandi, Zometa, Zytiga

Other safety concerns:

Duplicate therapy issues: Prolia contains denosumab, which is the same ingredient contained in Xgeva; patients receiving Xgeva should not be treated with Prolia

Adverse Reactions

A postmarketing safety program for Prolia is available to collect information on adverse events; more information is available at http://www.proliasafety.com. To report adverse events for either Prolia or Xgeva, prescribers may also call Amgen at 800-772-6436 or FDA at 800-332-1088.

Percentages noted with Prolia (60 mg every 6 months) unless specified as Xgeva (120 mg every 4 weeks):

>10%:

Cardiovascular: Hypertension (11%, Lewiecki 2007)

Central nervous system: Fatigue (Xgeva: ≤45%), headache (Xgeva: 13% to 24%), peripheral edema (5%; Xgeva: 24%)

Dermatologic: Dermatitis (4% to 11%), eczema (4% to 11%), skin rash (3% to 11%)

Endocrine & metabolic: Hypophosphatemia (Xgeva: 32%; grade 3: 10% to 15%), hypocalcemia (2%; Xgeva: 3% to 18%; grade 3: 3%)

Gastrointestinal: Nausea (Xgeva: 31%), decreased appetite (Xgeva: 24%), vomiting (Xgeva: 24%), constipation (Xgeva: 21%), diarrhea (Xgeva: 20%)

Hematologic & oncologic: Anemia (Xgeva: 21%)

Infection: Influenza (11%, Lewiecki 2007)

Neuromuscular & skeletal: Weakness (Xgeva: ≤45%), arthralgia (7% to 14%), limb pain (10% to 12%), back pain (8% to 12%)

Respiratory: Dyspnea (Xgeva: 21% to 27%), cough (Xgeva: 15%)

1% to 10%:

Cardiovascular: Angina pectoris (3%)

Central nervous system: Sciatica (5%)

Endocrine & metabolic: Hypercholesterolemia (7%)

Gastrointestinal: Flatulence (2%)

Hematologic & oncologic: Malignant neoplasm (new; 3% to 5%)

Infection: Serious infection (4%)

Neuromuscular & skeletal: Musculoskeletal pain (6%), ostealgia (4%), myalgia (3%), osteonecrosis (jaw; ≤2%; Xgeva ≤2%)

Ophthalmic: Cataract (≤5%)

Respiratory: Nasopharyngitis (7%), upper respiratory tract infection (5%)

<1%, postmarketing, and/or case reports: Anaphylaxis (both formulations), antibody development (both formulations), endocarditis, erythema, facial swelling, femur fracture (both formulations; diaphyseal, subtrochanteric), hearing loss (FDA Safety Alert June 6, 2016), hypercalcemia (Xgeva, following discontinuation), hypersensitivity (both formulations), hypotension, pancreatitis, severe hypocalcemia (symptomatic; both formulations), urticaria

Contraindications Hypersensitivity to denosumab or any component of the formulation; preexisting hypocalcemia; pregnancy (Prolia only)

Warnings/Precautions

Concerns related to adverse effects:

• Bone fractures: Atypical femur fractures have been reported in patients receiving denosumab. The fractures may occur anywhere along the femoral shaft (may be bilateral) and commonly occur with minimal to no trauma to the area. Some patients experience prodromal pain weeks or months before the fracture occurs. Because these fractures also occur in osteoporosis patients not treated with denosumab, it is unclear if denosumab therapy is the cause for the fractures; concomitant glucocorticoids may contribute to fracture risk. Advise patients to report new/unusual hip, thigh, or groin pain; and if so, evaluate for atypical/incomplete fracture. Contralateral limb should be assessed if atypical fracture occurs. Consider interrupting therapy in patients who develop an atypical femoral fracture. Following treatment discontinuation (in patients being treated for osteoporosis), the fracture risk increases, including risk of multiple vertebral fractures; vertebral fractures occurred as early as 7 months (average: 19 months) after the last dose of denosumab. Evaluate benefit/risk before initiating denosumab treatment for osteoporosis, especially in patients with prior vertebral fracture. If denosumab is discontinued, consider transitioning to an alternative osteoporosis therapy.

• Dermatologic reactions: Dermatitis, eczema, and rash (which are not necessarily specific to the injection site) have been reported. Consider discontinuing if severe symptoms occur.

• Hypersensitivity: Clinically significant hypersensitivity (including anaphylaxis) has been reported. May include throat tightness, facial edema, upper airway edema, lip swelling, dyspnea, pruritus, rash, urticaria, and hypotension. If anaphylaxis or clinically significant hypersensitivity occurs, initiate appropriate management and permanently discontinue.

• Hypercalcemia: Hypercalcemia (clinically significant) may occur in patients with growing skeletons weeks to months following discontinuation of denosumab therapy. Monitor for signs/symptoms of hypercalcemia (eg, nausea, vomiting, headache, decreased alertness) and treat accordingly.

• Hypocalcemia: Denosumab may cause or exacerbate hypocalcemia; severe symptomatic cases (including fatalities) have been reported. An increased risk has been observed with increasing renal dysfunction, most commonly severe dysfunction (creatinine clearance <30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels; correct preexisting hypocalcemia prior to therapy. Monitor levels more frequently when denosumab is administered with other drugs that can also lower calcium levels. Use caution in patients with a history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment/dialysis, or other conditions which would predispose the patient to hypocalcemia; monitor calcium, phosphorus, and magnesium closely during therapy (the manufacturer recommends monitoring within 14 days of injection [Prolia] or during the first weeks of therapy initiation [Xgeva]). Hypocalcemia lasting weeks to months (and requiring frequent monitoring) has been reported in postmarketing analyses. Administer calcium, vitamin D, and magnesium as necessary. Patients with severe renal impairment (CrCl <30 mL/minute) or those on dialysis may also develop marked elevations of serum parathyroid hormone (PTH).

• Infection: Incidence of infections may be increased, including serious skin infections, abdominal, urinary, ear, or periodontal infections. Endocarditis has also been reported following use. Patients should be advised to contact their healthcare provider if signs or symptoms of severe infection or cellulitis develop. Use with caution in patients with impaired immune systems or using concomitant immunosuppressive therapy; may be at increased risk for serious infections. Evaluate the need for continued treatment with serious infection.

• Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ), also referred to as medication-related osteonecrosis of the jaw (MRONJ), has been reported in patients receiving denosumab. ONJ may manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth/periodontal infection, toothache, gingival ulceration/erosion. Risk factors include invasive dental procedures (eg, tooth extraction, dental implants, oral surgery), cancer diagnosis, immunosuppressive therapy, angiogenesis inhibitor therapy, chemotherapy, systemic corticosteroids, poor oral hygiene, use of a dental appliance, ill-fitting dentures, periodontal and/or other pre-existing dental disease, diabetes and gingival infections, local infection with delayed healing, anemia, and/or coagulopathy. In studies of patients with osseous metastasis, a longer duration of denosumab exposure was associated with a higher incidence of ONJ, although a majority of patients had predisposing factors, including a history of poor oral hygiene, tooth extraction, or the use of a dental appliance. Patients should maintain good oral hygiene during treatment. A dental exam and appropriate preventive dentistry should be performed prior to therapy. The manufacturer’s labeling recommends avoiding invasive dental procedures in patients with bone metastases receiving denosumab for prevention of skeletal-related events and to consider temporary discontinuation of therapy in these patients if invasive dental

procedure is required. According to a position paper by the American Association of Maxillofacial Surgeons (AAOMS), MRONJ has been associated with bisphosphonates and other antiresorptive agents (denosumab), and antiangiogenic agents (eg, bevacizumab, sunitinib) used for the treatment of osteoporosis or malignancy; risk is significantly higher in cancer patients receiving antiresorptive therapy compared to patients receiving osteoporosis treatment (regardless of medication used or dosing schedule). MRONJ risk is increased with intravenous antiresorptive therapy compared to the minimal risk associated with oral bisphosphonate use, although risk appears to increase with oral bisphosphonates when duration of therapy exceeds 4 years. The AAOMS suggests that if medically permissible, initiation of denosumab for cancer therapy should be delayed until optimal dental health is attained (if extractions are required, antiresorptive therapy should delayed until the extraction site has mucosalized or until after adequate osseous healing). Once denosumab is initiated for oncologic disease, procedures that involve direct osseous injury and placement of dental implants should be avoided. Patients developing ONJ during therapy should receive care by an oral surgeon (AAOMS [Ruggiero 2014]). According to the manufacturer, discontinuation of denosumab should be considered (based on risk/benefit evaluation) in patients who develop ONJ.

• Musculoskeletal pain: Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported (time to onset of symptoms has varied from one day to several months after initiating therapy). Consider discontinuing use if severe symptoms develop.

Disease-related concerns:

• Breast cancer: The American Society of Clinical Oncology (ASCO) updated guidelines on the role of bone-modifying agents (BMAs) in the prevention and treatment of skeletal-related events for metastatic breast cancer patients (Van Poznak 2011). The guidelines recommend initiating a BMA (denosumab, pamidronate, zoledronic acid) in patients with metastatic breast cancer to the bone. There is currently no literature indicating the superiority of one particular BMA. Optimal duration is not defined; however, the guidelines recommend continuing therapy until substantial decline in patient's performance status. The ASCO guidelines are in alignment with package insert guidelines for dosing, renal dose adjustments, infusion times, prevention and management of osteonecrosis of the jaw, and monitoring of laboratory parameter recommendations. BMAs are not the first-line therapy for pain. BMAs are to be used as adjunctive therapy for cancer-related bone pain associated with bone metastasis, demonstrating a modest pain control benefit. BMAs should be used in conjunction with agents such as NSAIDs, opioid and nonopioid analgesics, corticosteroids, radiation/surgery, and interventional procedures.

• Multiple myeloma: Denosumab is not indicated for the prevention of skeletal-related events in patients with multiple myeloma. In trials of with multiple myeloma patients, denosumab was noninferior to zoledronic acid in delaying time to first skeletal–related event and mortality was increased in a subset of the denosumab-treated group.

• Renal impairment: Use with caution in patients with renal impairment (CrCl <30 mL/minute) or patients on dialysis; risk of hypocalcemia is increased. Dose adjustment is not needed when administered at 60 mg every 6 months (Prolia); once-monthly dosing has not been evaluated in patients with renal impairment (Xgeva).

Concomitant drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Dosage form specific issues:

• Latex: Packaging may contain natural latex rubber.

Special populations:

• Pediatric: May impair bone growth in children with open growth plates or inhibit eruption of dentition. Indicated only for the treatment of giant cell tumor of the bone in adolescents who are skeletally mature.

Other warnings/precautions:

• Administration: Denosumab is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally.

• Appropriate use: Postmenopausal osteoporosis: For use in women at high risk for fracture which is defined as a history of osteoporotic fracture or multiple risk factors for fracture. May also be used in women who failed or did not tolerate other therapies.

• Duplicate therapy: Do not administer Prolia and Xgeva to the same patient for different indications.

• Long-term therapy: Denosumab therapy results in significant suppression of bone turnover; the long-term effects of treatment are not known, but may contribute to adverse outcomes such as ONJ, atypical fractures, or delayed fracture healing; monitor.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Belimumab: Monoclonal Antibodies may enhance the adverse/toxic effect of Belimumab. *Risk X: Avoid combination*

Immunosuppressants: Denosumab may enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. **Exceptions:** Cytarabine (Liposomal). *Risk C: Monitor therapy*

Pregnancy Risk Factor

D (Xgeva)/X (Prolia) (show table)

Pregnancy Implications

Use of Prolia is contraindicated in pregnant women. Adverse events were observed in animal reproduction studies. Specifically, increased fetal loss, stillbirths, postnatal mortality, absent lymph nodes, abnormal bone growth, and decreased neonatal growth was observed in cynomolgus monkeys exposed to denosumab throughout pregnancy. Denosumab was measurable in the offspring at one month of age. Fetal exposure to monoclonal antibodies is expected to increase as pregnancy progresses. Women of reproductive potential should be advised to use effective contraception during denosumab treatment and for at least 5 months following the last dose. Studies of denosumab when used for osteoporosis/bone loss in men demonstrated that it is unlikely that a female partner or fetus would be exposed during unprotected sex to pharmacologically relevant denosumab concentrations via seminal fluid; however, exposure from seminal fluid of men receiving denosumab for other indications and higher doses is unknown and therefore their pregnant partners should be counseled regarding this potential risk.

Women exposed to denosumab during pregnancy should contact the Amgen Pregnancy Surveillance Program (800-772-6436).

Breast-Feeding Considerations It is not known if denosumab is excreted in breast milk. According to the manufacturer, the decision to discontinue denosumab or discontinue breast-feeding should take into account the benefits of treatment to the mother. In some animal studies, mammary gland development was impaired following exposure to denosumab during pregnancy, resulting in impaired lactation postpartum.

Dietary Considerations Ensure adequate calcium and vitamin D intake to prevent or treat hypocalcemia. Calcium 1000 mg/day and vitamin D ≥400 units/day is recommended in product labeling (Prolia). If dietary intake is inadequate, dietary supplementation is recommended. Women and men should consume:

Calcium: 1000 mg/day (men: 50 to 70 years) **or** 1200 mg/day (women ≥51 years and men ≥71 years) (IOM 2011; NOF 2014)

Vitamin D: 800 to 1000 units/day (men and women ≥50 years) (NOF 2014). Recommended Dietary Allowance (RDA): 600 units/day (men and women ≤70 years) **or** 800 units/day (men and women ≥71 years) (IOM 2011).

Monitoring Parameters Recommend monitoring of serum creatinine, serum calcium, phosphorus and magnesium (especially within the first 14 days of therapy [Prolia] or during the first weeks of therapy initiation [Xgeva]), signs and symptoms of hypocalcemia, especially in patients predisposed to hypocalcemia (severe renal impairment, thyroid/parathyroid surgery, malabsorption syndromes, hypoparathyroidism); signs/symptoms of hypercalcemia (following discontinuation in patients with growing skeletons); infection, or dermatologic reactions; routine oral exam (prior to treatment); dental exam if risk factors for ONJ; monitor for sings/symptoms of hypersensitivity

Osteoporosis: Bone mineral density (BMD) should be re-evaluated every 2 years (or more frequently) after initiating therapy (NOF 2014); annual measurements of height and weight, assessment of chronic back pain; serum calcium and 25(OH)D; may consider monitoring biochemical markers of bone turnover

Reference Range

Calcium (total): Adults: 9.0 to 11.0 mg/dL (2.05 to 2.54 mmol/L), may slightly decrease with aging

Phosphorus: 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L)

Vitamin D: There is no clear consensus on a reference range for total serum 25(OH)D concentrations or the validity of this level as it relates clinically to bone health. In addition, there is significant variability in the reporting of serum 25(OH)D levels as a result of different assay types in use; however, the following ranges have been suggested:

Adults (IOM 2011): Sufficient levels in practically all persons: ≥20 ng/mL (50 nmol/L); concern for risk of toxicity: >50 ng/mL (125 nmol/L)

Osteoporosis patients (NOF 2014): Recommended level to reach and maintain: ~30 ng/mL (75 nmol/L)

Mechanism of Action Denosumab is a monoclonal antibody with affinity for nuclear factor-kappa ligand (RANKL). Osteoblasts secrete RANKL; RANKL activates osteoclast precursors and subsequent osteolysis which promotes release of bone-derived growth factors, such as insulin-like growth factor-1 (IGF1) and transforming growth factor-beta (TGF-beta), and increases serum calcium levels. Denosumab binds to RANKL, blocks the interaction between RANKL and RANK (a receptor located on osteoclast surfaces), and prevents osteoclast formation, leading to decreased bone resorption and increased bone mass in osteoporosis. In solid tumors with bony metastases, RANKL inhibition decreases osteoclastic activity leading to decreased skeletal related events and tumor-induced bone destruction. In giant cell tumors of the bone (which express RANK and RANKL), denosumab inhibits tumor growth by preventing RANKL from activating its receptor (RANK) on the osteoclast surface, osteoclast precursors, and osteoclast-like giant cells.

Pharmacodynamics/Kinetics

Onset of action: Decreases markers of bone resorption by ~85% within 3 days; maximal reductions observed within 1 month

Hypercalcemia of malignancy: Time to response (median): 9 days; Time to complete response (median): 23 days (Hu 2014)

Duration: Markers of bone resorption return to baseline within 12 months of discontinuing therapy

Hypercalcemia of malignancy: Duration of response (median): 104 days; Duration of complete response (median): 34 days (Hu 2014)

Bioavailability: SubQ: 62%

Half-life elimination: ~25 to 28 days

Time to peak, serum: 10 days (range: 3 to 21 days)

Pricing: US

Solution (Prolia Subcutaneous)

60 mg/mL (1 mL): $1293.06

Solution (Xgeva Subcutaneous)

120 mg/1.7 mL (1.7 mL): $2512.80

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Pralia (JP); Prolia (AE, AR, AT, AU, BE, BR, CH, CL, CR, CY, CZ, DE, DK, DO, EC, EE, ES, FR, GB, GR, GT, HK, HN, HR, IL, IS, JO, KR, KW, LB, LT, LU, LV, MT, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PL, QA, RO, SA, SE, SG, SK, SV, TH, TR, TW, UA, UY); Ranmark (JP); Xgeva (AE, AR, AU, BE, CH, CR, CY, CZ, DE, DK, DO, EC, EE, ES, FR, GB, GT, HK, HN, HR, IE, JO, KR, LT, LU, LV, MT, MX, MY, NI, NL, NO, NZ, PA, PH, RO, SE, SG, SI, SK, SV, TR, UA)

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Topic 15575 Version 124.0