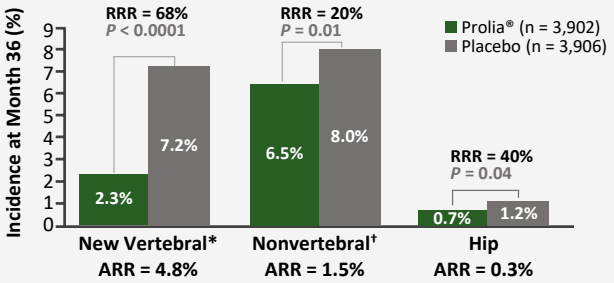
Prolia® (denosumab) Injection Clinical Fact Sheet

For Formulary and Managed Care Decision Makers

Efficacy in Women With Postmenopausal Osteoporosis (PMO) at High Risk for Fracture[1,2]

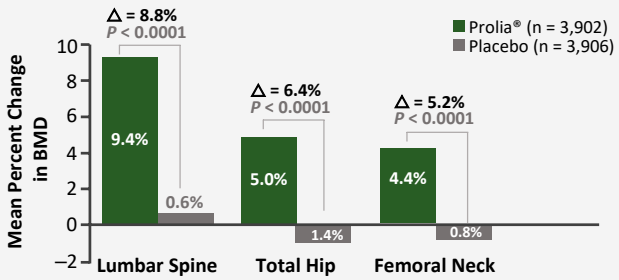
The pivotal phase 3 fracture trial included 7,808 women with PMO (mean age of 72 years), with bone mineral density (BMD) T-score < –2.5 and ≥ –4.0 at the lumbar spine (LS) or total hip. Patients were randomly assigned to receive Prolia® 60 mg subcutaneously (SC) or placebo once every 6 months (Q6M). All patients received supplemental calcium and vitamin D. The primary endpoint was the incidence of new vertebral fracture at 36 months.

Prolia® Significantly Reduced the Incidence of Vertebral, Nonvertebral, and Hip Fractures Versus Placebo at 3 Years[1,2]



ARR = absolute risk reduction; RRR = relative risk reduction.
*Calculated for 7,393 patients. The effect of Prolia® on the incidence of new vertebral fracture was also significant versus placebo at months 12 and 24.
†Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the skull, face, mandible, metacarpals, fingers, and toes.

Prolia® Significantly Increased BMD Versus Placebo at All Anatomic Sites Measured at 3 Years[1,3,‡]



Intent-to-treat, last-observation-carried-forward analysis.
BMD = bone mineral density.
‡After discontinuation, BMD returned to approximately baseline levels within 12 months.

Efficacy in Men With Osteoporosis at High Risk for Fracture[1,4]

The phase 3 trial included 242 men (mean age of 65 years) with LS or femoral neck (FN) BMD T-score ≤ –2.0 and ≥ –3.5, or with a previous major osteoporotic fracture and LS or FN BMD T-score ≤ –1.0 and ≥ –3.5, and at least two lumbar vertebrae, one femur, and one forearm evaluable by DXA. Patients were randomly assigned to receive Prolia® 60 mg SC or placebo Q6M. All patients received supplemental calcium and vitamin D. The primary endpoint was the percent change from baseline in LS BMD at 12 months.

Prolia® Significantly Increased LS BMD Versus Placebo at 12 Months[1,4]

BL = baseline; BMD = bone mineral density; LS = lumbar spine.
*$P < 0.0001$.

Indications

Prolia® is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia® reduces the incidence of vertebral, nonvertebral, and hip fractures.

Prolia® is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

Prolia® is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Prolia® is indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia® also reduced the incidence of vertebral fractures.

Prolia® is indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Contraindications: Prolia® is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia®. Prolia® is contraindicated in women who are pregnant and may cause fetal harm. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®. Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling and urticaria.

Efficacy in Men Receiving Androgen Deprivation Therapy (ADT) for Nonmetastatic Prostate Cancer[1,5]

The pivotal phase 3 trial included 1,468 men (median age of 76 years) with nonmetastatic prostate cancer receiving ADT, randomly assigned to receive Prolia® 60 mg SC or placebo Q6M. All patients received supplemental calcium and vitamin D.

The primary endpoint was the percent change in LS BMD from baseline to month 24. At month 24, change in LS BMD was higher for Prolia® (5.6%) versus placebo (–1.0%), $P < 0.0001$. A secondary endpoint was the incidence of new vertebral fracture at month 36. At month 36, Prolia® reduced the incidence of new vertebral fractures versus placebo (1.5% vs 3.9%, respectively). Relative risk reduction was 62% and absolute risk reduction was 2.4% for Prolia®.

Efficacy in Women Receiving Aromatase Inhibitor (AI) Therapy for Breast Cancer[1,6]

The pivotal phase 3 trial included 252 women (median age 59 years) with breast cancer receiving AI therapy, randomly assigned to receive Prolia® 60 mg SC or placebo Q6M. All patients received supplemental calcium and vitamin D. The primary endpoint was the percent change in LS BMD from baseline to month 12. At month 12, change in LS BMD was higher for Prolia® (4.8%) versus placebo (–0.7%), $P < 0.0001$.

Efficacy in Men and Women With Glucocorticoid-Induced Osteoporosis at High Risk for Fracture[1,7,8]

The phase 3 trial included 795 patients (505 glucocorticoid-continuing patients and 290 glucocorticoid-initiating patients) who were receiving glucocorticoids (≥ 7.5 mg oral prednisone or daily equivalent), randomly assigned to receive Prolia® 60 mg SC Q6M and oral placebo once daily (QD), or 5 mg oral risedronate QD and placebo SC Q6M. All patients received supplemental calcium and vitamin D. The primary endpoint was the noninferiority of Prolia® to risedronate with respect to percent change from baseline in LS BMD at month 12. At month 12, Prolia® significantly increased LS BMD compared with the active control in both the glucocorticoid-continuing (4.4% [95% confidence interval 3.8–5.0] vs 2.3% [1.7–2.9]) and glucocorticoid-initiating (3.8% [3.1–4.5] vs 0.8% [0.2–1.5]) subpopulations.

Please see additional Important Safety Information on reverse side.

AMGEN®

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Dosing and Administration[1]

Prolia® should be administered by a healthcare professional. The recommended dose of Prolia® is a 60 mg SC injection in the upper arm, upper thigh, or abdomen Q6M. Preexisting hypocalcemia must be corrected prior to initiating Prolia®. Adequately supplement all patients with calcium (1,000 mg daily) and vitamin D (≥ 400 IU daily). Pregnancy must be ruled out prior to administration of Prolia®. Multiple vertebral fractures have been reported following Prolia® discontinuation.

Mechanism of Action[1]

Prolia® is the first FDA-approved receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) inhibitor. Prolia® prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Pharmacologic Properties[1]

In clinical studies, treatment with Prolia® 60 mg reduced bone resorption, as measured by serum type 1 C-telopeptide (CTX), by ~85% by 3 days. Maximal reductions occurred by 1 month. At the end of each dosing interval, CTX reductions were partially attenuated from a maximal reduction of ≥ 87% to ≥ 45%, as serum denosumab levels diminished, reflecting the reversibility of the effects of Prolia® on bone remodeling.

Important Safety Information

Contraindications: Prolia® is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia®. Prolia® is contraindicated in women who are pregnant and may cause fetal harm. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®. Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling and urticaria.

Same Active Ingredient: Prolia® contains the same active ingredient (denosumab) found in XGEVA®. Patients receiving Prolia® should not receive XGEVA®.

Hypersensitivity: Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia®. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of Prolia®.

Hypocalcemia: Hypocalcemia may worsen with the use of Prolia®, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, including treatment with other calcium-lowering drugs, clinical monitoring of calcium and mineral levels is highly recommended within 14 days of Prolia® injection. Concomitant use of calcimimetic drugs may worsen hypocalcemia risk and serum calcium should be closely monitored. Adequately supplement all patients with calcium and vitamin D.

Osteonecrosis of the Jaw (ONJ): ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia®. An oral exam should be performed by the prescriber prior to initiation of Prolia®. A dental examination with appropriate preventive dentistry is recommended prior to treatment in patients with risk factors for ONJ such as invasive dental procedures, diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders. Good oral hygiene practices should be maintained during treatment with Prolia®. The risk of ONJ may increase with duration of exposure to Prolia®.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia® should be considered based on individual benefit-risk assessment.

Atypical Femoral Fractures: Atypical low-energy, or low trauma fractures of the shaft have been reported in patients receiving Prolia®. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with antiresorptive agents.

During Prolia® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be evaluated to rule out an incomplete femur fracture. Interruption of Prolia® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia® Treatment: Following discontinuation of Prolia® treatment, fracture risk increases, including the risk of multiple vertebral fractures. New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of Prolia®. Prior vertebral fracture was a predictor of multiple vertebral fractures after Prolia® discontinuation. Evaluate an individual's benefit/risk before initiating treatment with Prolia®. If Prolia® treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy.

Serious Infections: In a clinical trial (N=7808) in women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia® group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract and ear were more frequent in patients treated with Prolia®.

Endocarditis was also reported more frequently in Prolia®-treated patients. The incidence of opportunistic infections and the overall incidence of infections were similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia®, prescribers should assess the need for continued Prolia® therapy.

Dermatologic Adverse Reactions: In the same clinical trial in women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema and rashes occurred at a significantly higher rate with Prolia® compared to placebo. Most of these events were not specific to the injection site. Consider discontinuing Prolia® if severe symptoms develop.

Musculoskeletal Pain: Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking Prolia®. Consider discontinuing use if severe symptoms develop.

Suppression of Bone Turnover: In clinical trials in women with postmenopausal osteoporosis, Prolia® resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for these consequences, including ONJ, atypical fractures, and delayed fracture healing.

Adverse Reactions: The most common adverse reactions (>5% and more common than placebo) in women with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions (>5% and more common than placebo) in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. Pancreatitis has been reported with Prolia®.

In women with postmenopausal osteoporosis, the overall incidence of new malignancies was 4.3% in the placebo group and 4.8% in the Prolia® group. In men with osteoporosis, new malignancies were reported in no patients in the placebo group and 4 (3.3%) patients in the Prolia® group. A causal relationship to drug exposure has not been established.

The most common adverse reactions (>3% and more common than active-control group) in patients with glucocorticoid-induced osteoporosis are back pain, hypertension, bronchitis, and headache.

The most common (per patient incidence ≥10%) adverse reactions reported with Prolia® in patients with bone loss receiving ADT for prostate cancer or adjuvant AI therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. Additionally, in Prolia®-treated men with nonmetastatic prostate cancer receiving ADT, a greater incidence of cataracts was observed.

Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

Please see accompanying Prolia® full Prescribing Information, including Medication Guide.

1. Prolia® (denosumab) prescribing information, Amgen. 2. Cummings SR, et al. *N Engl J Med.* 2009;361:756-765. 3. Data on file, Amgen; 2008. 4. Orwoll E, et al. *J Clin Endocrinol Metab*. 2012;97:3161-3169. 5. Smith MR, et al. *N Engl J Med.* 2009;361:745-755. 6. Ellis GK, et al. *J Clin Oncol.* 2008;26:4875-4882. 7. Saag KG, et al. *Lancet Diabetes Endocrinol*. 2018;6:445-454. 8. Data on file, Amgen; 2016.

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