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 24.0 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

<table>
<thead>
<tr>
<th>Incidence at Month 36 (%)</th>
<th>New Vertebral*</th>
<th>Nonvertebral†</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR = 4.8%</td>
<td>2.3%</td>
<td>7.2%</td>
<td>6.5%</td>
</tr>
<tr>
<td>ARR = 1.5%</td>
<td>6.5%</td>
<td>8.0%</td>
<td>5.5%</td>
</tr>
<tr>
<td>ARR = 0.3%</td>
<td>0.7%</td>
<td>5.4%</td>
<td>4.4%</td>
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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® 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.

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

The pivotal phase 3 trial included 1,488 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 Men 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 242 men (mean age 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 all anatomic sites measured at 3 years.1,3,4

Efficacy in Women With Osteoporosis at High Risk for Fracture.1,4

The phase 3 trial included 242 women (mean age 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

Please see additional important safety information on reverse side.
Dosing and Administration

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. Pre-existing 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

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

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 include hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria. Allergic-like 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 diuretics or calcium-channel 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, fracture risk index 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 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 yet 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. 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 metastatic 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.

Pharmacologic Properties

In clinical studies, treatment with Prolia® 60 mg reduced bone resorption, as measured by serum type 1-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.

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