The following promotional message is brought to you by Amgen.

Learn more about a head-to-head bone mineral density (BMD) study comparing alendronate continuation to Prolia® in women with postmenopausal osteoporosis (PMO)

prolia® (denosumab) injection

INDICATION

Prolia® (denosumab) 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.

CONTRAINDICATIONS:

Prolia® is contraindicated in patients with hypocalcemia, women who are pregnant, and patients with a history of systemic hypersensitivity to any component of the product. Perform pregnancy testing in women of reproductive potential prior to initiating treatment with Prolia®.

Please scroll below for additional Important Safety Information.

Dear [Insert Customer Name],

FREEDOM: Pivotal Phase 3 Fracture Trial

PIVOTAL PHASE 3 FRACTURE TRIAL STUDY DESIGN[1,2]

A multicenter, international, randomized, double-blind, placebo-controlled clinical trial that studied postmenopausal women between 60 and 90 years of age with a BMD T-score between -2.5 and 4.0 at the lumbar spine or total hip.

7808 patients were randomized to receive Prolia® 60 mg (n = 3902) or placebo (n = 3906) subcutaneously every 6 months. All patients were supplemented with daily calcium and vitamin D.

PRIMARY ENDPOINT[1,2]

- Incidence of new vertebral fractures at 3 years

SECONDARY ENDPOINTS[1,2]

- Time to first nonvertebral fracture* and time to first hip fracture

*Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.

RESULTS OF THE PIVOTAL PHASE 3 FRACTURE TRIAL[1-3]

During the pivotal Phase 3 fracture trial in postmenopausal women with osteoporosis, Prolia® significantly reduced the relative risk of fracture at 3 years in vertebral (68%*), hip (40%†), and nonvertebral (20%‡) sites (vs placebo).

There were no significant differences between subjects who received denosumab and those who received placebo in the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events.

Adverse reactions most commonly reported (≥ 5% and more common than placebo) in the Prolia®-treated group were back pain (34.7%), pain in extremity (11.7%), musculoskeletal pain (7.6%), hypercholesterolemia (7.2%), and cystitis (5.9%).

*Absolute risk reduction: 4.8% ($P < 0.0001$).
†Absolute risk reduction: 0.3% ($P = 0.04$).
‡Absolute risk reduction: 1.5% ($P = 0.01$).

Review 3-Year Pivotal FREEDOM Study

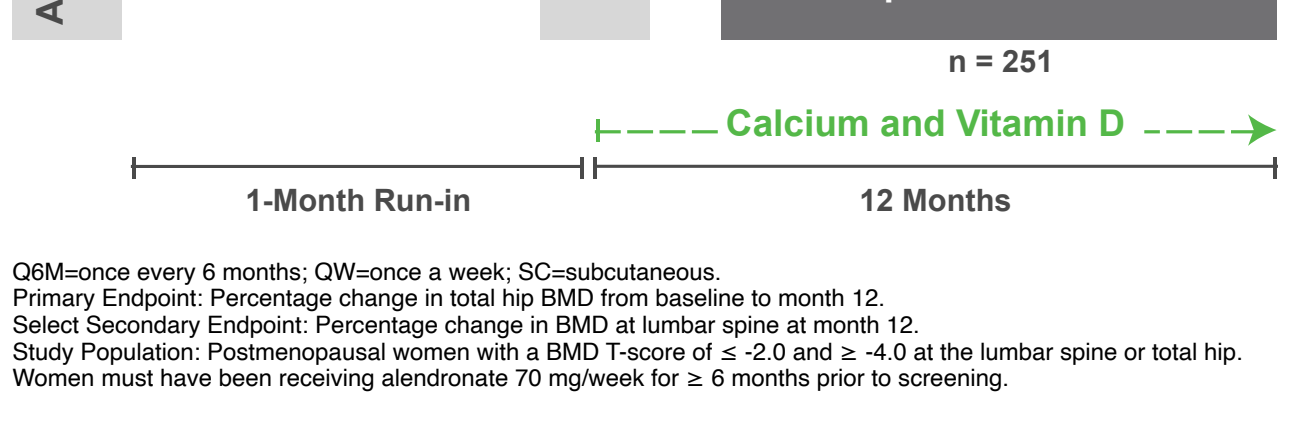
The efficacy and safety of Prolia® in female patients with PMO were further evaluated in a 7-year open-label extension study.[3] Long-term use of Prolia® has been studied for up to 10 years across the pivotal Phase 3 fracture trial and open-label extension study.[3]

Review Open-label Extension Study

STAND: Prolia® vs Alendronate

A head-to-head BMD study evaluated women with PMO continuing on alendronate or transitioning to Prolia® in a 1-year, multicenter, international, randomized, double-blind, double-dummy, parallel-group Phase 3 trial[4]

PATIENTS CONTINUING ON ALENDRONATE THERAPY OR TRANSITIONING TO PROLIA® WERE EVALUATED[4]

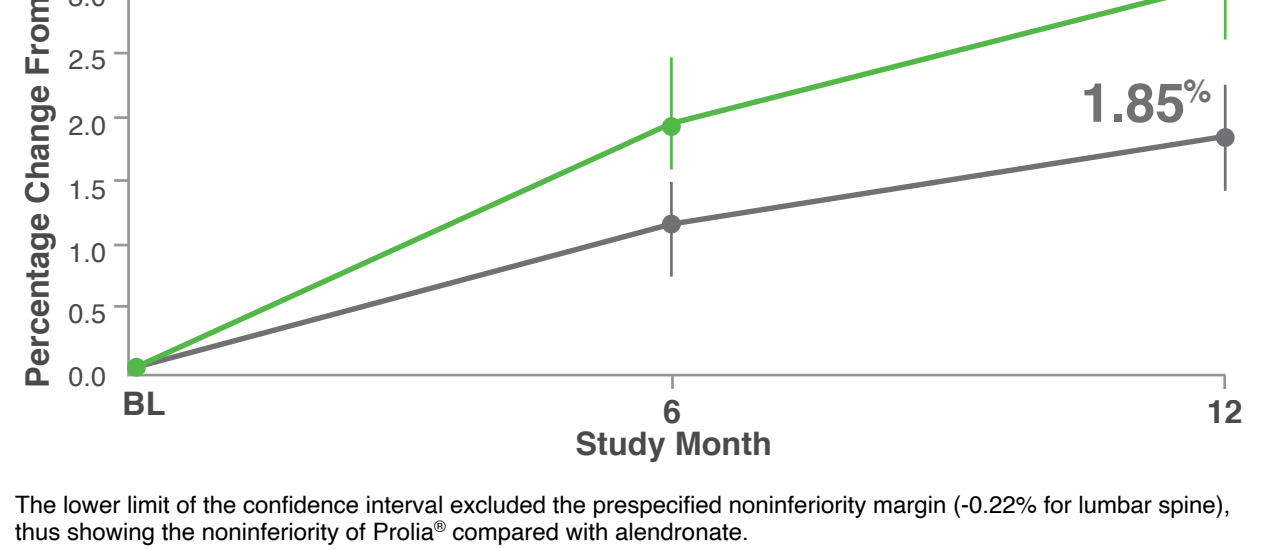


Q6M=once every 6 months; QW=once a week; SC=subcutaneous.
Primary Endpoint: Percentage change in total hip BMD from baseline to month 12.
Select Secondary Endpoint: Percentage change in BMD at lumbar spine at month 12.
Study Population: Postmenopausal women with a BMD T-score of ≤ -2.0 and ≥ -4.0 at the lumbar spine or total hip.
Women must have been receiving alendronate 70 mg/week for ≥ 6 months prior to screening.

PROLIA® DEMONSTRATED NONINFERIORITY AND SUPERIORITY (VS ALENDRONATE) IN TOTAL HIP BMD[4]

The lower limit of the confidence interval excluded the prespecified noninferiority margin (-0.35% for total hip), thus showing the noninferiority of Prolia® compared with alendronate.
Superiority testing demonstrated that the BMD increase with denosumab at the total hip was statistically superior to the change with alendronate ($P < 0.0001$).
*95% CI 0.44%-1.25%, $P < 0.01$.

PROLIA® DEMONSTRATED NONINFERIORITY (VS ALENDRONATE) AND SHOWED STATISTICALLY SIGNIFICANT CHANGES IN LUMBAR SPINE BMD[4,*]



The lower limit of the confidence interval excluded the prespecified noninferiority margin (-0.22% for lumbar spine), thus showing the noninferiority of Prolia® compared with alendronate.
*Secondary endpoint.
†95% CI 0.63%-1.73%, $P < 0.01$.

BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy. Head-to-head fracture studies have not been conducted.

A SIMILAR NUMBER OF STUDY PARTICIPANTS IN EACH TREATMENT GROUP REPORTED ADVERSE EVENTS DURING THE STUDY (78% PROLIA®, 79% ALENDRONATE)[4]

SUMMARY OF ADVERSE EVENTS

	Alendronate (N = 249) n (%)	Prolia® (denosumab) (N = 253) n (%)
Any adverse event	196 (78.7)	197 (77.9)
Leading to study discontinuation	2 (0.8)	3 (1.2)
Death	0 (0.0)	1 (0.4)
Selected adverse events		
Clinical fractures*	4 (1.6)	8 (3.2)
Gastrointestinal-related disorders	60 (24.1)	58 (22.9)
Infections	93 (37.3)	111 (43.9)
Neoplasms (benign or malignant)	9 (3.6)	9 (3.6)
Serious adverse events	16 (6.4)	15 (5.9)
Selected serious adverse events		
Infections	3 (1.2)	1 (0.4)
Neoplasms (benign or malignant)	3 (1.2)	3 (1.2)

The most frequent adverse events in the Prolia® and alendronate groups, respectively, were nasopharyngitis (13.4% and 10.8%), back pain (10.7% and 11.6%), bronchitis (6.3% and 5.6%), arthralgia (5.9% and 10.4%), constipation (5.1% and 4.8%), and pain in an extremity (4.7% and 8.4%).
*On-study clinical fractures were as follows: Prolia®—2 foot, 2 wrist, 1 radius, 1 fibula, 1 humerus, 1 pelvis, 1 rib, 1 tibia; alendronate—1 foot, 1 wrist, 1 radius, 1 sacrum.

Help lead your members to stronger bones with access to Prolia®.[1,4]
Please visit proliapayerresources.com for more information

IMPORTANT SAFETY INFORMATION

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), 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: 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: 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 consequences, including ONJ, atypical fractures, and delayed fracture healing.

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

The overall incidence of new malignancies was 4.3% in the placebo group and 4.8% in the Prolia® group. A causal relationship to drug exposure has not been established. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

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

References: **1.** Prolia® (denosumab) prescribing information, Amgen. **2.** Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-765. **3.** Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomized FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;5:513-523. **4.** Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res*. 2010;25:72-81.

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