Managed Healthcare[®]

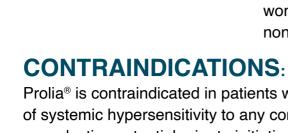


Prolia® (denosumab) significantly reduced the

risk of new vertebral, hip, and nonvertebral

For the treatment of postmenopausal women with osteoporosis at high risk for fracture.

fractures at 3 years. 1,2



PIVOTAL PHASE 3 STUDY DESIGN:

daily calcium and vitamin D.

PRIMARY ENDPOINT^{1,2}

women with osteoporosis, Prolia[®] reduces the incidence of vertebral, nonvertebral, and hip fractures.

INDICATION

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.

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

Dear [Insert Customer Name],

Multicenter, international, randomized, double-blind, placebo-controlled clinical trial that studied postmenopausal women between 60 years of age with a BMD T-score between -2.5 and -4.0 at

Evaluate incidence of new vertebral fractures at 3 years

SECONDARY ENDPOINTS^{1,2} Evaluate time to nonvertebral fractures and time to the first hip fractures

the lumbar spine or total hip. 7,808 patients were randomized to receive Prolia(R) 60 mg (n =

3,902) or placebo (n = 3,906) subcutaneously every 6 months. All patients were supplemented with

SCREENING

Percentage Change From Baseline in BMD

N = 7808

Placebo (n = 3906) Prolia[®] (n = 3902)

7.2%

2.3%

New Vertebral Fracture*

Year 3 (0-36 months)

 $(ARR^{\ddagger} = 4.8\%) P < 0.0001$

difference

Back pain

Cystitis

Vertigo

Anemia

Insomnia

Myalgia

Pain in extremity

Musculoskeletal pain

Hypercholesterolemia

Edema, peripheral

Abdominal pain, upper

Upper respiratory tract infection

†Relative risk reduction. [‡]Absolute risk reduction.

Spine BMD at 3 Years^{1,2}

RANDOMIZATION Study End Placebo n = 3906All subjects received daily calcium (≥ 1 g) and vitamin D (≥ 400 IU) supplementation 36 Months FRACTURE RELATIVE RISK REDUCTION VS PLACEBO^{1,3}

PIVOTAL STUDY DESIGN DETAILS^{1,3}

Denosumab 60 mg SC Q6M

n = 3902

Study End

Last dose month 30, followed until month 36

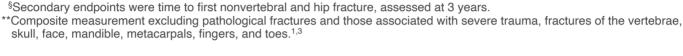
8.0%

6.5%

Nonvertebral Fracture^{9,***}

Year 3 [0-36 months]

 $[ARR^{\ddagger} = 1.5\%] P = 0.01$



*Includes 7393 patients with a baseline and at least one post-baseline radiograph

PROLIA® SIGNIFICANTLY INCREASED BONE MINERAL DENSITY (BMD) AT KEY SITES AT 3 YEARS¹ Significant Increase in Femoral Significant Increase in Total Hip Significant Increase in Lumbar Neck BMD at 3 Years^{1,2} BMD at 3 Years^{1,2}

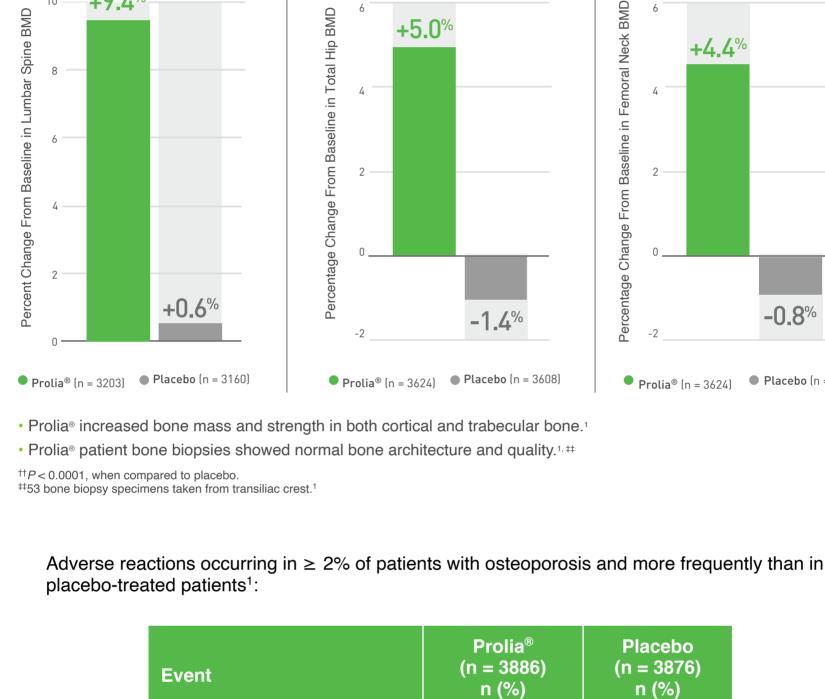
Prolia® is proven to significantly reduce fracture risk at vertebral, hip, and nonvertebral sites at 3 years in female patients with postmenopausal osteoporosis (PMO)^{1,3}

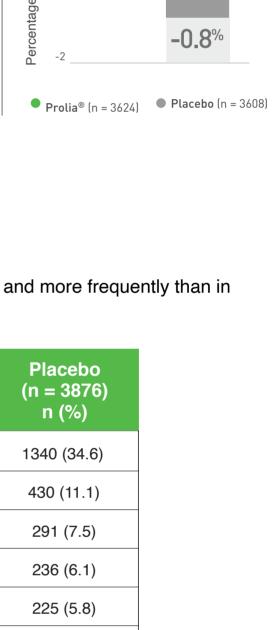
Hip Fracture§

Year 3 (0-36 months)

 $[ARR^{\ddagger} = 0.3\%] P = 0.04$

+5.0% +4.4%





187 (4.8)

167 (4.3)

155 (4.0)

111 (2.9)

107 (2.8)

122 (3.1)

94 (2.4)

Sciatica 178 (4.6) 149 (3.8) Pneumonia 152 (3.9) 150 (3.9) 142 (3.7) 117 (3.0) Bone pain

1347 (34.7)

453 (11.7)

297 (7.6)

280 (7.2)

228 (5.9)

195 (5.0)

190 (4.9)

189 (4.9)

129 (3.3)

129 (3.3)

126 (3.2)

114 (2.9)

87 (2.2) Angina pectoris 101 (2.6) Rash 96 (2.5) 79 (2.0) Pharyngitis 91 (2.3) 78 (2.0) 90 (2.3) Asthenia 73 (1.9) **Pruritus** 87 (2.2) 82 (2.1) Flatulence 84 (2.2) 53 (1.4) 64 (1.7) Spinal osteoarthritis 82 (2.1) Gastroesophageal reflux disease 80 (2.1) 66 (1.7) Atrial fibrillation 79 (2.0) 77 (2.0) Herpes zoster 79 (2.0) 72 (1.9) The most common adverse reactions (> 5% and more common than those seen with placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis.1 The efficacy and safety of Prolia® in female patients with PMO were further evaluated in a 7-year open-label extension study.1-4 **REVIEW STUDY ONLINE** Help lead your members to stronger bones with access to Prolia[®]. 1,5 Please visit <u>proliapayerresources.com</u> for more information. 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®.

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.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia® Treatment: Following

the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia[®].

specific to the injection site. Consider discontinuing Prolia® if severe symptoms develop.

reported in patients taking Prolia®. Consider discontinuing use if severe symptoms develop.

be considered based on individual benefit-risk assessment.

should be transitioned to an alternative antiresorptive therapy.

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

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

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

Interruption of Prolia® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

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

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

Endocarditis was also reported more frequently in Prolia®-treated patients. The incidence of opportunistic

oral exam should be performed by the prescriber prior to initiation of Prolia®. A dental examination with

calcium and vitamin D.

delayed fracture healing.

reported with Prolia®.

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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

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

Adverse Reactions: The most common adverse reactions (>5% and more common than placebo) are back

Musculoskeletal Pain: Severe and occasionally incapacitating bone, joint, and/or muscle pain has been

References: 1. Prolia® (denosumab) prescribing information, Amgen. 2. Data on File, Amgen. 2008. 3. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med.

2009;361:756-765. 4. Bone HG, Brandi ML, Brown JP, et al. Ten years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM extension trial. Presented at: American Society of Bone and Mineral Research; October

pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has been

9-12, 2015; Seattle, WA. 5. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Mineral Res. 2010;25:72-81. **AMGEN®** One Amgen Center Drive Thousand Oaks, CA 91320-1799