HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROLIA safely and effectively. See full prescribing information for PROLIA.

Prolia® (denosumab)
Injection, for subcutaneous use
Initial U.S. Approval: 2010

----------RECENT MAJOR CHANGES----------
- Warnings and Precautions (5.4) 8/2016
- Warnings and Precautions (5.6) 1/2017

----------INDICATIONS AND USAGE----------
Prolia is a RANK ligand (RANKL) inhibitor indicated for:
- Treatment of postmenopausal women with osteoporosis at high risk for fracture (1.1)
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture (1.2)
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer (1.3)
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer (1.4)

----------DOSAGE AND ADMINISTRATION----------
- Prolia should be administered by a healthcare professional (2.1)
- Administer 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen (2.1)
- Instruct patients to take calcium 1000 mg daily and at least 400 IU vitamin D daily (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Single-use prefilled syringe containing 60 mg in a 1 mL solution (3)

----------CONTRAINDICATIONS----------
- Hypocalcemia (4, 5.3)
- Pregnancy (4, 8.1)
- Known hypersensitivity to Prolia (4, 5.2)

----------WARNINGS AND PRECAUTIONS----------
- Same Active Ingredient: Patients receiving Prolia should not receive XGEVA® (5.1)
- Hypersensitivity including anaphylactic reactions may occur. Discontinue permanently if a clinically significant reaction occurs (5.2)
- Hypocalcemia: Must be corrected before initiating Prolia. May worsen, especially in patients with renal impairment. Adequately supplement patients with calcium and vitamin D (5.3)
- Osteonecrosis of the jaw: Has been reported with Prolia. Monitor for symptoms (5.4)
- Atypical femoral fractures: Have been reported. Evaluate patients with thigh or groin pain to rule out a femoral fracture (5.5)
- Multiple vertebral fractures have been reported following Prolia discontinuation. Consider transitioning to another antiresorptive agent if Prolia is discontinued (5.6)
- Serious infections including skin infections: May occur, including those leading to hospitalization. Advise patients to seek prompt medical attention if they develop signs or symptoms of infection, including cellulitis (5.7)
- Dermatologic reactions: Dermatitis, rashes, and eczema have been reported. Consider discontinuing Prolia if severe symptoms develop (5.8)
- Severe bone, joint, muscle pain may occur. Discontinue use if severe symptoms develop (5.9)
- Suppression of bone turnover: Significant suppression has been demonstrated. Monitor for consequences of bone oversuppression (5.10)

----------ADVERSE REACTIONS----------
- Postmenopausal osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has been reported in clinical trials (6.1)
- Male osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, arthralgia, and nasopharyngitis (6.1)
- Bone loss due to hormone ablation for cancer: Most common adverse reactions (≥ 10% and more common than placebo) were: arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Pediatric patients: Safety and efficacy not established (8.4)
- Renal impairment: No dose adjustment is necessary in patients with renal impairment. Patients with creatinine clearance < 30 mL/min or receiving dialysis are at risk for hypocalcemia. Supplement with calcium and vitamin D, and consider monitoring serum calcium (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

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 *[see Clinical Studies (14.1)]*.

1.2 Treatment to Increase Bone Mass in Men with Osteoporosis

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 *[see Clinical Studies (14.2)]*.

1.3 Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

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 *[see Clinical Studies (14.3)]*.

1.4 Treatment of Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

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 *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Prolia should be administered by a healthcare professional.

The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily *[see Warnings and Precautions (5.3)]*.

If a dose of Prolia is missed, administer the injection as soon as the patient is available. Thereafter, schedule injections every 6 months from the date of the last injection.

2.2 Preparation and Administration

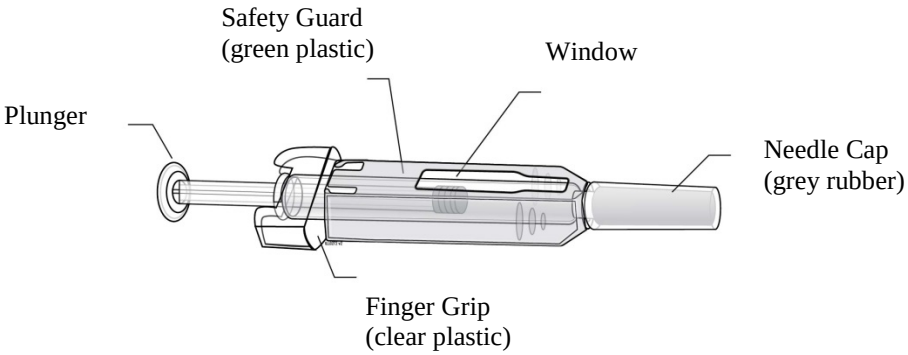
Visually inspect Prolia for particulate matter and discoloration prior to administration whenever solution and container permit. Prolia is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the solution contains many particles or foreign particulate matter.

Latex Allergy: People sensitive to latex should not handle the grey needle cap on the single-use prefilled syringe, which contains dry natural rubber (a derivative of latex).

Prior to administration, Prolia may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Prolia in any other way *[see How Supplied/Storage and Handling (16)]*.

Instructions for Prefilled Syringe with Needle Safety Guard
IMPORTANT: In order to minimize accidental needlesticks, the Prolia single-use prefilled syringe will have a green safety guard; manually activate the safety guard after the injection is given.

DO NOT slide the green safety guard forward over the needle before administering the injection; it will lock in place and prevent injection.

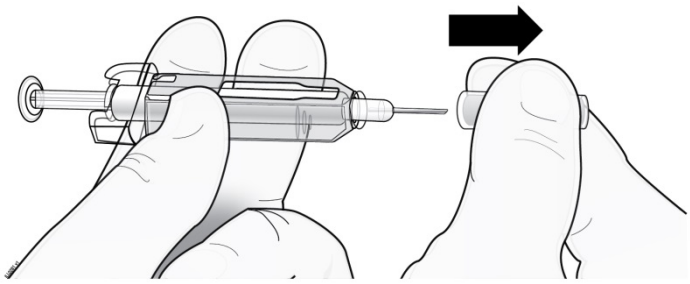


Activate the green safety guard (slide over the needle) after the injection.

The grey needle cap on the single-use prefilled syringe contains dry natural rubber (a derivative of latex); people sensitive to latex should not handle the cap.

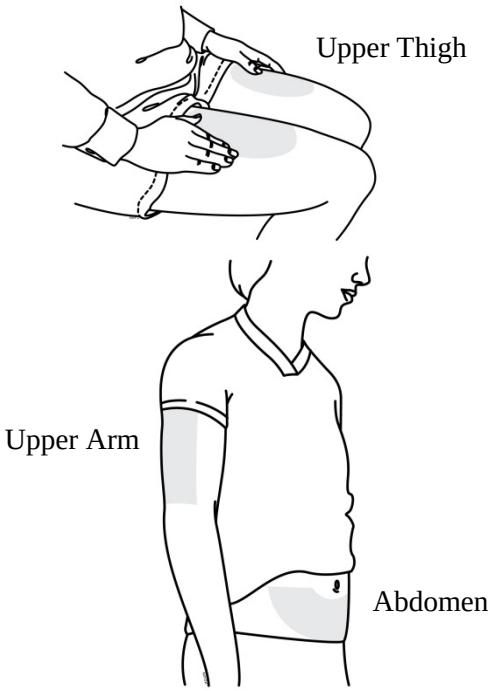
Step 1: Remove Grey Needle Cap

Remove needle cap.

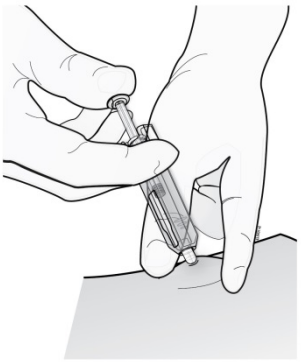


Step 2: Administer Subcutaneous Injection

Choose an injection site. The recommended injection sites for Prolia include: the upper arm OR the upper thigh OR the abdomen.



Insert needle and inject all the liquid subcutaneously. Do not administer into muscle or blood vessel.



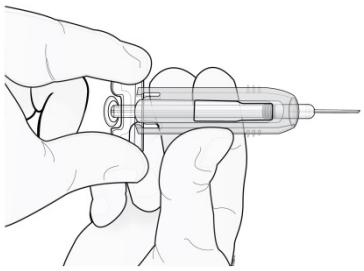
DO NOT put grey needle cap back on needle.

Step 3: Immediately Slide Green Safety Guard Over Needle

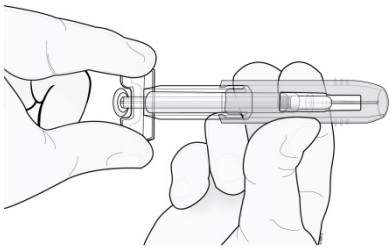
With the *needle pointing away from you…*

Hold the prefilled syringe by the clear plastic finger grip with one hand. Then, with the other hand, grasp the green safety guard by its base and gently slide it towards the needle until the green safety guard locks securely in place and/or you hear a "click." **DO NOT** grip the green safety guard too firmly - it will move easily if you hold and slide it gently.

Hold clear finger grip.



Gently slide green safety guard over needle and lock securely in place. Do not grip green safety guard too firmly when sliding over needle.



Immediately dispose of the syringe and needle cap in the nearest sharps container. **DO NOT** put the needle cap back on the used syringe.

3 DOSAGE FORMS AND STRENGTHS

- 1 mL of a 60 mg/mL solution in a single-use prefilled syringe

4 CONTRAINDICATIONS

Prolia is contraindicated in:

- Hypocalcemia: Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia *[see Warnings and Precautions (5.3)]*.
- Pregnancy: Prolia may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.
- Hypersensitivity: 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 *[see Warnings and Precautions (5.2), Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with Same Active Ingredient

Prolia contains the same active ingredient (denosumab) found in Xgeva. Patients receiving Prolia should not receive Xgeva.

5.2 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 *[see Contraindications (4), Adverse Reactions (6.2)]*.

5.3 Hypocalcemia and Mineral Metabolism

Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended within 14 days of Prolia injection. In some postmarketing cases, hypocalcemia persisted for weeks or months and required frequent monitoring and intravenous and/or oral calcium replacement, with or without vitamin D.

Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis. These patients may also develop marked elevations of serum parathyroid hormone (PTH). Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation.

Adequately supplement all patients with calcium and vitamin D *[see Dosage and Administration (2.1), Contraindications (4), Adverse Reactions (6.1), and Patient Counseling Information (17.3)]*.

5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. ONJ has been reported in patients receiving denosumab *[see Adverse Reactions (6.1)]*. A routine oral exam should be performed by the prescriber prior to initiation of Prolia treatment. A dental examination with appropriate preventive dentistry is recommended prior to treatment with Prolia in patients with risk factors for ONJ such as invasive dental procedures (e.g. tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g. chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment with Prolia. Concomitant administration of drugs associated with ONJ may increase the risk of developing ONJ. The risk of ONJ may increase with duration of exposure to Prolia.

For patients requiring invasive dental procedures, clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit-risk assessment.

Patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia therapy should be considered based on individual benefit-risk assessment.

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving Prolia *[see Adverse Reactions (6.1)]*. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-resorptive agents.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral, and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

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 suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Prolia therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.6 Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment

Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. Cessation of Prolia treatment results in markers of bone resorption increasing above pretreatment values then returning to pretreatment values 24 months after the last dose of Prolia. In addition, bone mineral density returns to pretreatment values within 18 months after the last injection. *[see Pharmacodynamics (12.2) and Clinical Studies (14.1)]*.

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, consider transitioning to an alternative antiresorptive therapy *[see Adverse Reactions (6.1)]*.

5.7 Serious Infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group *[see Adverse Reactions (6.1)]*. 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 was similar between placebo and Prolia groups, and the overall incidence of infections was 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. Consider the benefit-risk profile in such patients before treating with Prolia. In patients who develop serious infections while on Prolia, prescribers should assess the need for continued Prolia therapy.

5.8 Dermatologic Adverse Reactions

In a large clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the Prolia group compared to the placebo group. Most of these events were not specific to the injection site *[see Adverse Reactions (6.1)]*. Consider discontinuing Prolia if severe symptoms develop.

5.9 Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking Prolia *[see Adverse Reactions (6.2)]*. The time to onset of symptoms varied from one day to several months after starting Prolia. Consider discontinuing use if severe symptoms develop *[see Patient Counseling Information (17.9)]*.

5.10 Suppression of Bone Turnover

In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry *[see Clinical Pharmacology (12.2) and Clinical Studies (14.1)]*. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and also elsewhere in the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.3)]*
- Serious Infections *[see Warnings and Precautions (5.7)]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions (5.8)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.4)]*
- Atypical Subtrochanteric and Diaphyseal Femoral Fractures *[see Warnings and Precautions (5.5)]*
- Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment *[see Warnings and Precautions (5.6)]*

The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis.

The most common adverse reactions reported with Prolia in men with osteoporosis are back pain, arthralgia, and nasopharyngitis.

The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials.

The most common adverse reactions leading to discontinuation of Prolia in patients with postmenopausal osteoporosis are back pain and constipation.

To report Adverse Reactions with Prolia®, please call Amgen Medical Information at 1-800-772-6436, email medinfo@amgen.com, or report the event at FDA MedWatch.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Treatment of Postmenopausal Women with Osteoporosis

The safety of Prolia in the treatment of postmenopausal osteoporosis was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years. A total of 3876 women were exposed to placebo and 3886 women were exposed to Prolia administered subcutaneously once every 6 months as a single 60 mg dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 2.3% (n = 90) in the placebo group and 1.8% (n = 70) in the Prolia group. The incidence of nonfatal serious adverse events was 24.2% in the placebo group and 25.0% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 2.1% and 2.4% for the placebo and Prolia groups, respectively.

Adverse reactions reported in ≥ 2% of postmenopausal women with osteoporosis and more frequently in the Prolia-treated women than in the placebo-treated women are shown in the table below.

Table1. Adverse Reactions Occurring in ≥ 2% of Patients with Osteoporosis and More Frequently than in Placebo-treated Patients

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	129 (3.3)	107 (2.8)
CARDIAC DISORDERS		
Angina pectoris	101 (2.6)	87 (2.2)
Atrial fibrillation	79 (2.0)	77 (2.0)
EAR AND LABYRINTH DISORDERS		
Vertigo	195 (5.0)	187 (4.8)
GASTROINTESTINAL DISORDERS		
Abdominal pain upper	129 (3.3)	111 (2.9)
Flatulence	84 (2.2)	53 (1.4)
Gastroesophageal reflux disease	80 (2.1)	66 (1.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema peripheral	189 (4.9)	155 (4.0)
Asthenia	90 (2.3)	73 (1.9)

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
INFECTIONS AND INFESTATIONS		
Cystitis	228 (5.9)	225 (5.8)
Upper respiratory tract infection	190 (4.9)	167 (4.3)
Pneumonia	152 (3.9)	150 (3.9)
Pharyngitis	91 (2.3)	78 (2.0)
Herpes zoster	79 (2.0)	72 (1.9)
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolemia	280 (7.2)	236 (6.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	1347 (34.7)	1340 (34.6)
Pain in extremity	453 (11.7)	430 (11.1)
Musculoskeletal pain	297 (7.6)	291 (7.5)
Bone pain	142 (3.7)	117 (3.0)
Myalgia	114 (2.9)	94 (2.4)
Spinal osteoarthritis	82 (2.1)	64 (1.7)
NERVOUS SYSTEM DISORDERS		
Sciatica	178 (4.6)	149 (3.8)
PSYCHIATRIC DISORDERS		
Insomnia	126 (3.2)	122 (3.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	96 (2.5)	79 (2.0)
Pruritus	87 (2.2)	82 (2.1)

Hypocalcemia
Decreases in serum calcium levels to less than 8.5 mg/dL at any visit were reported in 0.4% women in the placebo group and 1.7% women in the Prolia group. The nadir in serum calcium level occurs at approximately day 10 after Prolia dosing in subjects with normal renal function.

In clinical studies, subjects with impaired renal function were more likely to have greater reductions in serum calcium levels compared to subjects with normal renal function. In a study of 55 subjects with varying degrees of renal function, serum calcium levels < 7.5 mg/dL or symptomatic hypocalcemia were observed in 5 subjects. These included no subjects in the normal renal function group, 10% of subjects in the creatinine clearance 50 to 80 mL/min group, 29% of subjects in the creatinine clearance < 30 mL/min group, and 29% of subjects in the hemodialysis group. These subjects did not receive calcium and vitamin D supplementation. In a study of 4550 postmenopausal women with osteoporosis, the mean

change from baseline in serum calcium level 10 days after Prolia dosing was -5.5% in subjects with creatinine clearance < 30 mL/min vs. -3.1% in subjects with creatinine clearance ≥ 30 mL/min.

Serious Infections
Receptor activator of nuclear factor kappa-B ligand (RANKL) is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, a RANKL inhibitor such as Prolia may increase the risk of infection.

In the clinical study of 7808 postmenopausal women with osteoporosis, the incidence of infections resulting in death was 0.2% in both placebo and Prolia treatment groups. However, the incidence of nonfatal serious infections was 3.3% in the placebo and 4.0% in the Prolia groups. Hospitalizations due to serious infections in the abdomen (0.7% placebo vs. 0.9% Prolia), urinary tract (0.5% placebo vs. 0.7% Prolia), and ear (0.0% placebo vs. 0.1% Prolia) were reported. Endocarditis was reported in no placebo patients and 3 patients receiving Prolia.

Skin infections, including erysipelas and cellulitis, leading to hospitalization were reported more frequently in patients treated with Prolia (< 0.1% placebo vs. 0.4% Prolia).

The incidence of opportunistic infections was similar to that reported with placebo.

Dermatologic Reactions
A significantly higher number of patients treated with Prolia developed epidermal and dermal adverse events (such as dermatitis, eczema, and rashes), with these events reported in 8.2% of the placebo and 10.8% of the Prolia groups ($p < 0.0001$). Most of these events were not specific to the injection site *[see Warnings and Precautions (5.8)]*.

Osteonecrosis of the Jaw
ONJ has been reported in the osteoporosis clinical trial program in patients treated with Prolia *[see Warnings and Precautions (5.4)]*.

Atypical Subtrochanteric and Diaphyseal Fractures
In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with Prolia. The duration of Prolia exposure to time of atypical femoral fracture diagnosis was as early as 2½ years *[see Warnings and Precautions (5.5)]*.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment
In the osteoporosis clinical trial program, multiple vertebral fractures were reported in patients after discontinuation of Prolia. In the phase 3 trial in women with postmenopausal osteoporosis, 6% of women who discontinued Prolia and remained in the study developed new vertebral fractures, and 3% of women who discontinued Prolia and remained in the study developed multiple new vertebral fractures. The mean time to onset of multiple vertebral fractures was 17 months (range: 7-43 months) after the last injection of Prolia. Prior vertebral fracture was a predictor of multiple vertebral fractures after discontinuation *[see Warnings and Precautions (5.6)]*.

Pancreatitis
Pancreatitis was reported in 4 patients (0.1%) in the placebo and 8 patients (0.2%) in the Prolia groups. Of these reports, 1 patient in the placebo group and all 8 patients in the Prolia group had serious events, including one death in the Prolia group. Several patients had a prior history of pancreatitis. The time from product administration to event occurrence was variable.

New Malignancies
The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia groups. New malignancies related to the breast (0.7% placebo vs. 0.9% Prolia), reproductive system (0.2% placebo vs. 0.5% Prolia), and gastrointestinal system (0.6% placebo vs. 0.9% Prolia) were reported. A causal relationship to drug exposure has not been established.

Treatment to Increase Bone Mass in Men with Osteoporosis

The safety of Prolia in the treatment of men with osteoporosis was assessed in a 1-year randomized, double-blind, placebo-controlled study. A total of 120 men were exposed to placebo and 120 men were exposed to Prolia administered subcutaneously once every 6 months as a single 60 mg dose. All men were instructed to take at least 1000 mg of calcium and 800 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 0.8% (n = 1) in the placebo group and 0.8% (n = 1) in the Prolia group. The incidence of nonfatal serious adverse events was 7.5% in the placebo group and 8.3% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 0% and 2.5% for the placebo and Prolia groups, respectively.

Adverse reactions reported in ≥ 5% of men with osteoporosis and more frequently with Prolia than in the placebo-treated patients were: back pain (6.7% placebo vs. 8.3% Prolia), arthralgia (5.8% placebo vs. 6.7% Prolia), and nasopharyngitis (5.8% placebo vs. 6.7% Prolia).

Serious Infections
Serious infection was reported in 1 patient (0.8%) in the placebo group and no patients in the Prolia group.

Dermatologic Reactions
Epidermal and dermal adverse events (such as dermatitis, eczema, and rashes) were reported in 4 patients (3.3%) in the placebo group and 5 patients (4.2%) in the Prolia group.

Osteonecrosis of the Jaw
No cases of ONJ were reported.

Pancreatitis
Pancreatitis was reported in 1 patient (0.8%) in the placebo group and 1 patient (0.8%) in the Prolia group.

New Malignancies
New malignancies were reported in no patients in the placebo group and 4 (3.3%) patients (3 prostate cancers, 1 basal cell carcinoma) in the Prolia group.

Treatment of Bone Loss in Patients Receiving Androgen Deprivation Therapy for Prostate Cancer or Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

The safety of Prolia in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 1468 men aged 48 to 97 years. A total of 725 men were exposed to placebo and 731 men were exposed to Prolia administered once every 6 months as a single 60 mg subcutaneous dose. All men were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of serious adverse events was 30.6% in the placebo group and 34.6% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 6.1% and 7.0% for the placebo and Prolia groups, respectively.

The safety of Prolia in the treatment of bone loss in women with nonmetastatic breast cancer receiving aromatase inhibitor (AI) therapy was assessed in a 2-year, randomized, double-blind, placebo-controlled, multinational study of 252 postmenopausal women aged 35 to 84 years. A total of 120 women were exposed to placebo and 129 women were exposed to Prolia administered once every 6 months as a single 60 mg subcutaneous dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of serious adverse events was 9.2% in the placebo group and 14.7% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 4.2% and 0.8% for the placebo and Prolia groups, respectively.

Adverse reactions reported in ≥ 10% of Prolia-treated patients receiving ADT for prostate cancer or adjuvant AI therapy for breast cancer, and more frequently than in the placebo-treated patients were: arthralgia (13.0% placebo vs. 14.3% Prolia) and back pain (10.5% placebo vs. 11.5% Prolia). Pain in extremity (7.7% placebo vs. 9.9% Prolia) and musculoskeletal pain (3.8% placebo vs. 6.0% Prolia) 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 (1.2% placebo vs. 4.7% Prolia). Hypocalcemia (serum calcium < 8.4 mg/dL) was reported only in Prolia-treated patients (2.4% vs. 0%) at the month 1 visit.

6.2 Postmarketing Experience

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post approval use of Prolia:

- Drug-related hypersensitivity reactions: anaphylaxis, rash, urticaria, facial swelling, and erythema
- Hypocalcemia: severe symptomatic hypocalcemia
- Musculoskeletal pain, including severe cases
- Parathyroid Hormone (PTH): Marked elevation in serum PTH in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis.
- Multiple vertebral fractures following discontinuation of Prolia

6.3 Immunogenicity

Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% (55 out of 8113) of patients treated with Prolia for up to 5 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients tested positive for neutralizing antibodies, as was assessed using a chemiluminescent cell-based in vitro biological assay. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was associated with binding antibody development.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result may be influenced by several factors, including assay methodology, sample handling, timing of sample

collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

In subjects with postmenopausal osteoporosis, Prolia (60 mg subcutaneous injection) did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4), indicating that it should not affect the pharmacokinetics of drugs metabolized by this enzyme in this population *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolia is contraindicated for use in pregnant women because it may cause harm to a fetus. There are insufficient data with denosumab use in pregnant women to inform any drug-associated risks for adverse developmental outcomes. In utero denosumab exposure from cynomolgus monkeys dosed monthly with denosumab throughout pregnancy at a dose 50-fold higher than the recommended human dose based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality, and absent lymph nodes, abnormal bone growth, and decreased neonatal growth *(see Data)*.

Data

Animal Data

The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANK ligand (RANKL) expression was turned off by gene removal (a “knockout mouse”). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy starting at gestational day 20 and at a pharmacologically active dose 50-fold higher than the recommended human dose based on body weight, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia, and tooth malalignment; and decreased neonatal growth. At birth out to 1 month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels).

Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated. Mammary gland histopathology at 6 months of age was normal in female offspring exposed to denosumab in utero; however, development and lactation have not been fully evaluated.

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.2) and Nonclinical Toxicology (13.2)]*.

The no-effect dose for denosumab-induced teratogenicity is unknown. However, a C_{max} of 22.9 ng/mL was identified in cynomolgus monkeys as a level in which no biologic effects (NOEL) of denosumab were observed (no inhibition of RANKL) *[see Clinical Pharmacology (12.3)]*.

8.2 Lactation

Risk Summary

There is no information regarding the presence of denosumab in human milk, the effects on the breastfed infant, or the effects on milk production. Denosumab was detected in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab (≤ 0.5% milk:serum ratio) and maternal mammary gland development was normal, with no impaired lactation. However, pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.1), Nonclinical Toxicology (13.2)]*.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Denosumab was present at low concentrations (approximately 2% of serum exposure) in the seminal fluid of male subjects given Prolia. Following vaginal intercourse, the maximum amount of denosumab delivered to a female partner would result in exposures approximately 11,000 times lower than the prescribed 60 mg subcutaneous dose, and at least 38 times lower than the NOEL in monkeys.

Therefore, male condom use would not be necessary as it is unlikely that a female partner or fetus would be exposed to pharmacologically relevant concentrations of denosumab via seminal fluid *[see Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

Prolia is not recommended in pediatric patients. The safety and effectiveness of Prolia in pediatric patients have not been established.

Treatment with Prolia may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (the target of Prolia therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 10 and 50 times (10 and 50 mg/kg dose) higher than the recommended human dose of 60 mg administered every 6 months, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab.

Cynomolgus monkeys exposed in utero to denosumab exhibited bone abnormalities, an absence of axillary, inguinal, mandibular, and mesenteric lymph nodes, reduced hematopoiesis, tooth malalignment, and decreased neonatal growth. Some bone abnormalities recovered once exposure was ceased following birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth *[see Use in Specific Populations (8.1)]*.

8.5 Geriatric Use

Of the total number of patients in clinical studies of Prolia, 9943 patients (76%) were ≥ 65 years old, while 3576 (27%) were ≥ 75 years old. Of the patients in the osteoporosis study in men, 133 patients (55%) were ≥ 65 years old, while 39 patients (16%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment.

In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcemia. Consider the benefit-risk profile when administering Prolia to patients with severe renal impairment or receiving dialysis. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis *[see Warnings and Precautions (5.3), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of Prolia.

10 OVERDOSAGE

There is no experience with overdosage with Prolia.

11 DESCRIPTION

Prolia (denosumab) is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Prolia is a sterile, preservative-free, clear, colorless to pale yellow solution.

Each 1 mL single-use prefilled syringe of Prolia contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prolia binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. 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.

12.2 Pharmacodynamics

In clinical studies, treatment with 60 mg of Prolia resulted in reduction in the bone resorption marker serum type 1 C-telopeptide (CTX) by approximately 85% by 3 days, with maximal reductions occurring by 1 month. CTX levels were below the limit of assay quantitation (0.049 ng/mL) in 39% to 68% of patients 1 to 3 months after dosing of Prolia. At the end of each dosing interval, CTX reductions were partially attenuated from a maximal reduction of ≥ 87% to ≥ 45% (range: 45% to 80%), as serum denosumab levels diminished, reflecting the reversibility of the effects of Prolia on bone remodeling. These effects were sustained with continued treatment. Upon reinitiation, the degree of inhibition of CTX by Prolia was similar to that observed in patients initiating Prolia treatment.

Consistent with the physiological coupling of bone formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers (i.e. osteocalcin and procollagen type 1 N-terminal peptide [PlNP]) were observed starting 1 month after the first dose of Prolia. After discontinuation of Prolia therapy, markers of bone resorption increased to levels 40% to 60% above pretreatment values but returned to baseline levels within 12 months.

12.3 Pharmacokinetics

In a study conducted in healthy male and female volunteers (n = 73, age range: 18 to 64 years) following a single subcutaneously administered Prolia dose of 60 mg after fasting (at least for 12 hours), the mean maximum denosumab concentration (C_{max}) was 6.75 mcg/mL (standard deviation [SD] = 1.89 mcg/mL). The median time to maximum denosumab concentration (T_{max}) was 10 days (range: 3 to 21 days). After C_{max}, serum denosumab concentrations declined over a period of 4 to 5 months with a mean half-life of 25.4 days (SD = 8.5 days; n = 46). The mean area-under-the-concentration-time curve up to 16 weeks ($AUC_{0\text{-}16\ weeks}$) of denosumab was 316 mcg·day/mL (SD = 101 mcg·day/mL).

No accumulation or change in denosumab pharmacokinetics with time was observed upon multiple dosing of 60 mg subcutaneously administered once every 6 months.

Prolia pharmacokinetics were not affected by the formation of binding antibodies.

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis showed no notable differences in pharmacokinetics with age (in postmenopausal women), race, or body weight (36 to 140 kg).

Seminal Fluid Pharmacokinetic Study

Serum and seminal fluid concentrations of denosumab were measured in 12 healthy male volunteers (age range: 43-65 years). After a single 60 mg subcutaneous administration of denosumab, the mean (± SD) C_{max} values in the serum and seminal fluid samples were 6170 (± 2070) and 100 (± 81.9) ng/mL, respectively, resulting in a maximum seminal fluid concentration of approximately 2% of serum levels. The median (range) T_{max} values in the serum and seminal fluid samples were 8.0 (7.9 to 21) and 21 (8.0 to 49) days, respectively. Among the subjects, the highest denosumab concentration in seminal fluid was 301 ng/mL at 22 days post-dose. On the first day of measurement (10 days post-dose), nine of eleven subjects had quantifiable concentrations in semen. On the last day of measurement (106 days post-dose), five subjects still had quantifiable concentrations of denosumab in seminal fluid, with a mean (± SD) seminal fluid concentration of 21.1 (± 36.5) ng/mL across all subjects (n = 12).

Drug Interactions

In a study of 17 postmenopausal women with osteoporosis, midazolam (2 mg oral) was administered 2 weeks after a single dose of denosumab (60 mg subcutaneous injection), which approximates the T_{max}

of denosumab. Denosumab did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the pharmacokinetics of drugs metabolized by CYP3A4 in postmenopausal women with osteoporosis.

Specific Populations
Gender: Mean serum denosumab concentration-time profiles observed in a study conducted in healthy men ≥ 50 years were similar to those observed in a study conducted in postmenopausal women using the same dose regimen.

Age: The pharmacokinetics of denosumab were not affected by age across all populations studied whose ages ranged from 28 to 87 years.

Race: The pharmacokinetics of denosumab were not affected by race.

Renal Impairment: In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab; thus, dose adjustment for renal impairment is not necessary.

Hepatic Impairment: No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.

Mutagenicity
The genotoxic potential of denosumab has not been evaluated.

Impairment of Fertility
Denosumab had no effect on female fertility or male reproductive organs in monkeys at doses that were 13- to 50-fold higher than the recommended human dose of 60 mg subcutaneously administered once every 6 months, based on body weight (mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Denosumab is an inhibitor of osteoclastic bone resorption via inhibition of RANKL.

In ovariectomized monkeys, once-monthly treatment with denosumab suppressed bone turnover and increased bone mineral density (BMD) and strength of cancellous and cortical bone at doses 50-fold higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight (mg/kg). Bone tissue was normal with no evidence of mineralization defects, accumulation of osteoid, or woven bone.

Because the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered (“knockout”) mice or use of other biological inhibitors of the RANK/RANKL pathway, namely OPG-Fc, provided additional information on the pharmacodynamic properties of denosumab. RANK/RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development

during pregnancy). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc also showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued.

14 CLINICAL STUDIES

14.1 Postmenopausal Women with Osteoporosis

The efficacy and safety of Prolia in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled trial. Enrolled women had a baseline BMD T-score between -2.5 and -4.0 at either the lumbar spine or total hip. Women with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 7808 enrolled women were aged 60 to 91 years with a mean age of 72 years. Overall, the mean baseline lumbar spine BMD T-score was -2.8, and 23% of women had a vertebral fracture at baseline. Women were randomized to receive subcutaneous injections of either placebo (N = 3906) or Prolia 60 mg (N = 3902) once every 6 months. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically-diagnosed) vertebral fractures at 3 years. Vertebral fractures were diagnosed based on lateral spine radiographs (T4-L4) using a semiquantitative scoring method. Secondary efficacy variables included the incidence of hip fracture and nonvertebral fracture, assessed at 3 years.

Effect on Vertebral Fractures

Prolia significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$), as shown in Table 2. The incidence of new vertebral fractures at year 3 was 7.2% in the placebo-treated women compared to 2.3% for the Prolia-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at year 3.

Table 2. The Effect of Prolia on the Incidence of New Vertebral Fractures in Postmenopausal Women

	Proportion of Women With Fracture (%)[+]		Absolute Risk Reduction (%)[*] (95% CI)	Relative Risk Reduction (%)[*] (95% CI)
	Placebo N = 3691 (%)	Prolia N = 3702 (%)		
0-1 Year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)
0-2 Years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)
0-3 Years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)

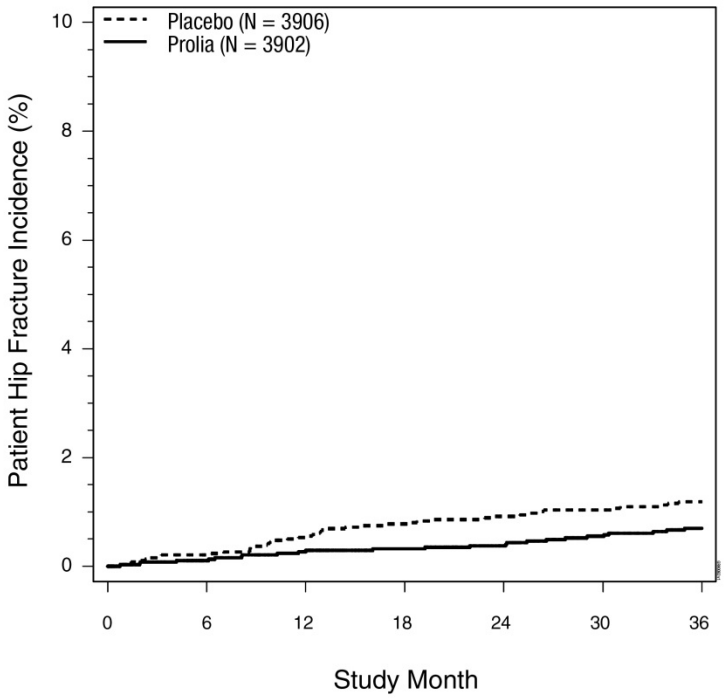
[+] Event rates based on crude rates in each interval.
[*] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group variable.

Prolia was effective in reducing the risk for new morphometric vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis.

Effect on Hip Fractures

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for Prolia-treated women at year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years (p = 0.04) (Figure 1).

Figure 1. Cumulative Incidence of Hip Fractures Over 3 Years



N = number of subjects randomized

Effect on Nonvertebral Fractures

Treatment with Prolia resulted in a significant reduction in the incidence of nonvertebral fractures (Table 3).

Table 3. The Effect of Prolia on the Incidence of Nonvertebral Fractures at Year 3

	Proportion of Women With Fracture (%)[+]		Absolute Risk Reduction (%) (95% CI)	Relative Risk Reduction (%) (95% CI)
	Placebo N = 3906 (%)	Prolia N = 3902 (%)		
Nonvertebral fracture[1]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)[*]

[+] Event rates based on Kaplan-Meier estimates at 3 years.
[1] Excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, and finger and toe phalanges.
[*] p-value = 0.01.

Effect on Bone Mineral Density (BMD)

Treatment with Prolia significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at

the femoral neck. Consistent effects on BMD were observed at the lumbar spine, regardless of baseline age, race, weight/body mass index (BMI), baseline BMD, and level of bone turnover.

After Prolia discontinuation, BMD returned to approximately baseline levels within 12 months.

Bone Histology and Histomorphometry
A total of 115 transiliac crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either month 24 and/or month 36 (53 specimens in Prolia group, 62 specimens in placebo group). Of the biopsies obtained, 115 (100%) were adequate for qualitative histology and 7 (6%) were adequate for full quantitative histomorphometry assessment.

Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with Prolia.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with Prolia, 35% had no tetracycline label present at the month 24 biopsy and 38% had no tetracycline label present at the month 36 biopsy, while 100% of placebo-treated patients had double label present at both time points. When compared to placebo, treatment with Prolia resulted in virtually absent activation frequency and markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

14.2 Treatment to Increase Bone Mass in Men with Osteoporosis

The efficacy and safety of Prolia in the treatment to increase bone mass in men with osteoporosis was demonstrated in a 1-year, randomized, double-blind, placebo-controlled trial. Enrolled men had a baseline BMD T-score between -2.0 and -3.5 at the lumbar spine or femoral neck. Men with a BMD T-score between -1.0 and -3.5 at the lumbar spine or femoral neck were also enrolled if there was a history of prior fragility fracture. Men with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that may affect bone were excluded from this study. The 242 men enrolled in the study ranged in age from 31 to 84 years with a mean age of 65 years. Men were randomized to receive SC injections of either placebo (n = 121) or Prolia 60 mg (n = 121) once every 6 months. All men received at least 1000 mg calcium and at least 800 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to 1 year. Secondary efficacy variables included percent change in total hip, and femoral neck BMD from baseline to 1 year.

Treatment with Prolia significantly increased BMD at 1 year. The treatment differences in BMD at 1 year were 4.8% (+0.9% placebo, +5.7% Prolia; (95% CI: 4.0, 5.6); $p < 0.0001$) at the lumbar spine, 2.0% (+0.3% placebo, +2.4% Prolia) at the total hip, and 2.2% (0.0% placebo, +2.1% Prolia) at femoral neck. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, BMD, testosterone concentrations, and level of bone turnover.

Bone Histology and Histomorphometry
A total of 29 transiliac crest bone biopsy specimens were obtained from men with osteoporosis at 12 months (17 specimens in Prolia group, 12 specimens in placebo group). Of the biopsies obtained, 29 (100%) were adequate for qualitative histology and, in Prolia patients, 6 (35%) were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments showed normal

architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with Prolia. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with Prolia, 6% had no tetracycline label present at the month 12 biopsy, while 100% of placebo pa-treated tients had double label present. When compared to placebo, treatment with Prolia resulted in markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

14.3 Treatment of Bone Loss in Men with Prostate Cancer

The efficacy and safety of Prolia in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) were demonstrated in a 3-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Men less than 70 years of age had either a BMD T-score at the lumbar spine, total hip, or femoral neck between -1.0 and -4.0, or a history of an osteoporotic fracture. The mean baseline lumbar spine BMD T-score was -0.4, and 22% of men had a vertebral fracture at baseline. The 1468 men enrolled ranged in age from 48 to 97 years (median 76 years). Men were randomized to receive subcutaneous injections of either placebo (n = 734) or Prolia 60 mg (n = 734) once every 6 months for a total of 6 doses. Randomization was stratified by age (< 70 years vs. ≥ 70 years) and duration of ADT at trial entry (≤ 6 months vs. > 6 months). Seventy-nine percent of patients received ADT for more than 6 months at study entry. All men received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)

The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 24. An additional key secondary efficacy variable was the incidence of new vertebral fracture through month 36 diagnosed based on x-ray evaluation by two independent radiologists. Lumbar spine BMD was higher at 2 years in Prolia-treated patients as compared to placebo-treated patients [-1.0% placebo, +5.6% Prolia; treatment difference 6.7% (95% CI: 6.2, 7.1); $p < 0.0001$].

With approximately 62% of patients followed for 3 years, treatment differences in BMD at 3 years were 7.9% (-1.2% placebo, +6.8% Prolia) at the lumbar spine, 5.7% (-2.6% placebo, +3.2% Prolia) at the total hip, and 4.9% (-1.8% placebo, +3.0% Prolia) at the femoral neck. Consistent effects on BMD were observed at the lumbar spine in relevant subgroups defined by baseline age, BMD, and baseline history of vertebral fracture.

Effect on Vertebral Fractures

Prolia significantly reduced the incidence of new vertebral fractures at 3 years ($p = 0.0125$), as shown in Table 4.

Table 4. The Effect of Prolia on the Incidence of New Vertebral Fractures in Men with Nonmetastatic Prostate Cancer

	Proportion of Men With Fracture (%)[+]		Absolute Risk Reduction (%)[*] (95% CI)	Relative Risk Reduction (%)[*] (95% CI)
	Placebo N = 673 (%)	Prolia N = 679 (%)		
0-1 Year	1.9	0.3	1.6 (0.5, 2.8)	85 (33, 97)
0-2 Years	3.3	1.0	2.2 (0.7, 3.8)	69 (27, 86)
0-3 Years	3.9	1.5	2.4 (0.7, 4.1)	62 (22, 81)

[+] Event rates based on crude rates in each interval.
[*] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group and ADT duration variables.

14.4 Treatment of Bone Loss in Women with Breast Cancer

The efficacy and safety of Prolia in the treatment of bone loss in women receiving adjuvant aromatase inhibitor (AI) therapy for breast cancer was assessed in a 2-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25. The mean baseline lumbar spine BMD T-score was -1.1, and 2.0% of women had a vertebral fracture at baseline. The 252 women enrolled ranged in age from 35 to 84 years (median 59 years). Women were randomized to receive subcutaneous injections of either placebo (n = 125) or Prolia 60 mg (n = 127) once every 6 months for a total of 4 doses. Randomization was stratified by duration of adjuvant AI therapy at trial entry (≤ 6 months vs. > 6 months). Sixty-two percent of patients received adjuvant AI therapy for more than 6 months at study entry. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 12. Lumbar spine BMD was higher at 12 months in Prolia-treated patients as compared to placebo-treated patients [-0.7% placebo, +4.8% Prolia; treatment difference 5.5% (95% CI: 4.8, 6.3); $p < 0.0001$].

With approximately 81% of patients followed for 2 years, treatment differences in BMD at 2 years were 7.6% (-1.4% placebo, +6.2% Prolia) at the lumbar spine, 4.7 % (-1.0% placebo, +3.8% Prolia) at the total hip, and 3.6% (-0.8% placebo, +2.8% Prolia) at the femoral neck.

16 HOW SUPPLIED/STORAGE AND HANDLING

Prolia is supplied in a single-use prefilled syringe with a safety guard. The grey needle cap on the single-use prefilled syringe contains dry natural rubber (a derivative of latex).

60 mg/1 mL in a single-use prefilled syringe	1 per carton	NDC 55513-710-01

Store Prolia in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Prior to administration, Prolia may be allowed to reach room temperature (up to 25°C/77°F) in the original container. Once removed from the refrigerator, Prolia must not be exposed to temperatures above 25°C/77°F and must be used within 14 days. If not used within the 14 days, Prolia should be discarded. Do not use Prolia after the expiry date printed on the label.
Protect Prolia from direct light and heat.

Avoid vigorous shaking of Prolia.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

17.1 Drug Products with Same Active Ingredient

Advise patients that denosumab is also marketed as Xgeva, and if taking Prolia, they should not receive Xgeva *[see Warnings and Precautions (5.1)]*.

17.2 Hypersensitivity

Advise patients to seek prompt medical attention if signs or symptoms of hypersensitivity reactions occur. Advise patients who have had signs or symptoms of systemic hypersensitivity reactions that they should not receive denosumab (Prolia or Xgeva) *[see Warnings and Precautions (5.2), Contraindications (4)]*.

17.3 Hypocalcemia

Adequately supplement patients with calcium and vitamin D and instruct them on the importance of maintaining serum calcium levels while receiving Prolia *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*. Advise patients to seek prompt medical attention if they develop signs or symptoms of hypocalcemia.

17.4 Osteonecrosis of the Jaw

Advise patients to maintain good oral hygiene during treatment with Prolia and to inform their dentist prior to dental procedures that they are receiving Prolia. Patients should inform their physician or dentist if they experience persistent pain and/or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.4)]*.

17.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Advise patients to report new or unusual thigh, hip, or groin pain *[see Warnings and Precautions (5.5)]*.

17.6 Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment

Advise patients not to interrupt Prolia therapy without talking to their physician *[see Warnings and Precautions (5.6)]*.

17.7 Serious Infections

Advise patients to seek prompt medical attention if they develop signs or symptoms of infections, including cellulitis *[see Warnings and Precautions (5.7)]*.

17.8 Dermatologic Reactions

Advise patients to seek prompt medical attention if they develop signs or symptoms of dermatological reactions (dermatitis, rashes, and eczema) *[see Warnings and Precautions (5.8)]*.

17.9 Musculoskeletal Pain

Inform patients that severe bone, joint, and/or muscle pain have been reported in patients taking Prolia. Patients should report severe symptoms if they develop *[see Warnings and Precautions (5.9)]*.

17.10 Pregnancy

Advise patients that Prolia is contraindicated in women who are pregnant and may cause fetal harm *[see Contraindications (4), Use in Specific Populations (8.1)]*.

17.11 Schedule of Administration

If a dose of Prolia is missed, administer the injection as soon as convenient. Thereafter, schedule injections every 6 months from the date of the last injection.

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: http://pat.amgen.com/prolia/

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MEDICATION GUIDE
Prolia® (PRÓ-lee-a)
(denosumab)
Injection, for subcutaneous use

What is the most important information I should know about Prolia?

If you receive Prolia, you should not receive XGEVA®. Prolia contains the same medicine as Xgeva (denosumab).

Prolia can cause serious side effects including:

- **Serious allergic reactions.** Serious allergic reactions have happened in people who take Prolia. Call your doctor or go to your nearest emergency room right away if you have any symptoms of a serious allergic reaction. Symptoms of a serious allergic reaction may include:
  - low blood pressure (hypotension)
  - trouble breathing
  - throat tightness
  - swelling of your face, lips, or tongue
  - rash
  - itching
  - hives
- **Low calcium levels in your blood (hypocalcemia).** Prolia may lower the calcium levels in your blood. If you have low blood calcium before you start receiving Prolia, it may get worse during treatment. Your low blood calcium must be treated before you receive Prolia. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:
  - spasms, twitches, or cramps in your muscles
  - numbness or tingling in your fingers, toes, or around your mouth

  Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Prolia. Take calcium and vitamin D as your doctor tells you to.
- **Severe jaw bone problems (osteonecrosis).** Severe jaw bone problems may happen when you take Prolia. Your doctor should examine your mouth before you start Prolia. Your doctor may tell you to see your dentist before you start Prolia. It is important for you to practice good mouth care during treatment with Prolia. Ask your doctor or dentist about good mouth care if you have any questions.
- **Unusual thigh bone fractures.** Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture include new or unusual pain in your hip, groin, or thigh.
- **Increased risk of broken bones, including broken bones in the spine, after stopping Prolia.** After your treatment with Prolia is stopped, your risk for breaking bones, including bones in your spine, is increased. Your risk for having more than 1 broken bone in your spine is increased if you have already had a broken bone in your spine. Do not stop taking Prolia without first talking with your doctor. If your Prolia treatment is stopped, talk to your doctor about other medicine that you can take.
- **Serious infections.** Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen if you take Prolia. Inflammation of the inner lining of the heart (endocarditis) due to an infection also may happen more often in people who take Prolia. You may need to go to the hospital for treatment if you develop an infection.

  Prolia is a medicine that may affect the ability of your body to fight infections. People who have a weakened immune system or take medicines that affect the immune system may have an increased risk for developing serious infections. Call your doctor right away if you have any of the following symptoms of infection:
  - fever or chills
  - skin that looks red or swollen and is hot or tender to touch
  - fever, shortness of breath, cough that will not go away
  - severe abdominal pain
  - frequent or urgent need to urinate or burning feeling when you urinate
- **Skin problems.** Skin problems such as inflammation of your skin (dermatitis), rash, and eczema may happen if you take Prolia. Call your doctor if you have any of the following symptoms of skin problems that do not go away or get worse:
  - redness
  - itching
  - small bumps or patches (rash)
  - your skin is dry or feels like leather
  - blisters that ooze or become crusty
  - skin peeling
- **Bone, joint, or muscle pain.** Some people who take Prolia develop severe bone, joint, or muscle pain.

Call your doctor right away if you have any of these side effects.

What is Prolia?

Prolia is a prescription medicine used to:

- Treat osteoporosis (thinning and weakening of bone) in women after menopause (“change of life”) who:
  - are at high risk for fracture (broken bone)
  - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
- Increase bone mass in men with osteoporosis who are at high risk for fracture.
- Treat bone loss in men who are at high risk for fracture receiving certain treatments for prostate cancer that has not spread to other parts of the body.
- Treat bone loss in women who are at high risk for fracture receiving certain treatments for breast cancer that has not spread to

other parts of the body.

It is not known if Prolia is safe and effective in children.

Do not take Prolia if you:

- have been told by your doctor that your blood calcium level is too low.
- are pregnant or plan to become pregnant.
- are allergic to denosumab or any of the ingredients in Prolia. See the end of this leaflet for a complete list of ingredients in Prolia.

Before taking Prolia, tell your doctor about all of your medical conditions, including if you:

- are taking a medicine called Xgeva (denosumab). Xgeva contains the same medicine as Prolia.
- have low blood calcium.
- cannot take daily calcium and vitamin D.
- had parathyroid or thyroid surgery (glands located in your neck).
- have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome).
- have kidney problems or are on kidney dialysis.
- plan to have dental surgery or teeth removed.
- are pregnant or plan to become pregnant. Prolia may harm your unborn baby. Tell your doctor right away if you become pregnant while taking Prolia.
- are breastfeeding or plan to breastfeed. It is not known if Prolia passes into your breast milk. You and your doctor should decide if you will take Prolia or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of medicines with you to show to your doctor or pharmacist when you get a new medicine.

How will I receive Prolia?

- Prolia is an injection that will be given to you by a healthcare professional. Prolia is injected under your skin (subcutaneous).
- You will receive Prolia 1 time every 6 months.
- You should take calcium and vitamin D as your doctor tells you to while you receive Prolia.
- If you miss a dose of Prolia, you should receive your injection as soon as you can.
- Take good care of your teeth and gums while you receive Prolia. Brush and floss your teeth regularly.
- Tell your dentist that you are receiving Prolia before you have dental work.

What are the possible side effects of Prolia?

Prolia may cause serious side effects.

- See **"What is the most important information I should know about Prolia?"**
- It is not known if the use of Prolia over a long period of time may cause slow healing of broken bones.

The most common side effects of Prolia in women who are being treated for osteoporosis after menopause are:

- back pain
- pain in your arms and legs
- high cholesterol
- muscle pain
- bladder infection

The most common side effects of Prolia in men with osteoporosis are:

- back pain
- joint pain
- common cold (runny nose or sore throat)

The most common side effects of Prolia in patients receiving certain treatments for prostate or breast cancer are:

- joint pain
- back pain
- pain in your arms and legs
- muscle pain

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Prolia.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Prolia if I need to pick it up from a pharmacy?

- Keep Prolia in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton.
- Do not freeze Prolia.
- When you remove Prolia from the refrigerator, Prolia must be kept at room temperature [up to 77°F (25°C)] in the original carton and must be used within 14 days.
- Do not keep Prolia at temperatures above 77°F (25°C). Warm temperatures will affect how Prolia works.
- Do not shake Prolia.
- Keep Prolia in the original carton to protect from light.

Keep Prolia and all medicines out of the reach of children.

General information about the safe and effective use of Prolia.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Prolia for a condition for which it was not prescribed. Do not give Prolia to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about Prolia that is written for health professionals.

What are the ingredients in Prolia?

Active ingredient: denosumab
Inactive ingredients: sorbitol, acetate, polysorbate 20, Water for Injection (USP), and sodium hydroxide

Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320-1799

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For more information, go to www.Prolia.com or call Amgen at 1-800-772-6436.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 05/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XGEVA® safely and effectively. See full prescribing information for XGEVA.

Xgeva (denosumab) injection, for subcutaneous use
Initial U.S. Approval: 2010

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Embryo-Fetal Toxicity (5.7) 05/2017

----------INDICATIONS AND USAGE----------

Xgeva is a RANK ligand (RANKL) inhibitor indicated for:

- Prevention of skeletal-related events in patients with bone metastases from solid tumors (1.1)
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (1.2, 14.2)
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (1.3)

Limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma

----------DOSAGE AND ADMINISTRATION----------

- Xgeva is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally (2.1)
- Bone Metastasis from Solid Tumors: Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen (2.2)
- Giant Cell Tumor of Bone: Administer 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen (2.3)
- Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia (2.2, 2.3)
- Hypercalcemia of Malignancy: Administer 120 mg every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 120 mg/1.7 mL (70 mg/mL) solution in a single-use vial (3)

----------CONTRAINDICATIONS----------

- Hypocalcemia (4.1)
- Known clinically significant hypersensitivity to Xgeva (4.2)

----------WARNINGS AND PRECAUTIONS----------

- Same Active Ingredient: Patients receiving Xgeva should not take Prolia® (5.1)
- Hypersensitivity reactions including anaphylaxis may occur. Discontinue permanently if a clinically significant reaction occurs (5.2)
- Hypocalcemia: Xgeva can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct hypocalcemia prior to initiating Xgeva. Monitor calcium levels during therapy, especially in the first weeks of initiating therapy, and adequately supplement all patients with calcium and vitamin D (5.3)
- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Xgeva. Perform an oral examination prior to starting Xgeva. Monitor for symptoms. Avoid invasive dental procedures during treatment with Xgeva (5.4)
- Atypical femoral fracture: Evaluate patients with thigh or groin pain to rule out a femoral fracture (5.5)
- Hypercalcemia Following Treatment Discontinuation in Patients with Growing Skeletons: Monitor patients for signs and symptoms of hypercalcemia and treat appropriately.(5.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use effective contraception (5.7, 8.1, 8.3)

----------ADVERSE REACTIONS----------

- Bone Metastasis from Solid Tumors: Most common adverse reactions (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (6.1)
- Giant Cell Tumor of Bone: Most common adverse reactions (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity (6.1)
- Hypercalcemia of Malignancy: Adverse reactions in greater than 20% of patients were nausea, dyspnea, decreased appetite, headache, peripheral edema, vomiting, anemia, constipation, and diarrhea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric patients: Recommended only for treatment of skeletally mature adolescents with giant cell tumor of bone (8.4)
- Renal impairment: Patients with creatinine clearance less than 30 mL/min or receiving dialysis are at risk for hypocalcemia. Adequately supplement with calcium and vitamin D (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bone Metastasis from Solid Tumors

Xgeva is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

Limitation of Use:
Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma *[see Clinical Trials (14.1)]*.

1.2 Giant Cell Tumor of Bone

Xgeva is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

1.3 Hypercalcemia of Malignancy

Xgeva is indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy *[see Clinical Trials (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Xgeva is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally.

2.2 Bone Metastasis from Solid Tumors

The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen.

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia *[see Warnings and Precautions (5.3)]*.

2.3 Giant Cell Tumor of Bone

The recommended dose of Xgeva is 120 mg administered every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen.

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia *[see Warnings and Precautions (5.3)]*.

2.4 Hypercalcemia of Malignancy

The recommended dose of Xgeva is 120 mg administered every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen.

2.5 Preparation and Administration

Visually inspect Xgeva for particulate matter and discoloration prior to administration. Xgeva is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the solution contains many particles or foreign particulate matter.

Prior to administration, Xgeva may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Xgeva in any other way *[see How Supplied/Storage and Handling (16)]*.

Use a 27-gauge needle to withdraw and inject the entire contents of the vial. Do not re-enter the vial. Discard vial after single-use or entry.

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/1.7 mL (70 mg/mL) solution in a single-use vial.

4 CONTRAINDICATIONS

4.1 Hypocalcemia

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Xgeva *[see Warnings and Precautions (5.3)]*.

4.2 Hypersensitivity

Xgeva is contraindicated in patients with known clinically significant hypersensitivity to Xgeva *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with Same Active Ingredient

Xgeva includes the same active ingredient (denosumab) found in Prolia. Patients receiving Xgeva should not take Prolia.

5.2 Hypersensitivity

Clinically significant hypersensitivity including anaphylaxis has been reported with use of Xgeva. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue Xgeva therapy permanently *[see Contraindications (4.2) and Adverse Reactions (6.2)]*.

5.3 Hypocalcemia

Xgeva can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct pre-existing hypocalcemia prior to Xgeva treatment. Monitor calcium levels, throughout Xgeva therapy, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when Xgeva is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare provider for symptoms of hypocalcemia *[see Contraindications (4.1), Adverse Reactions (6.1, 6.2), and Patient Counseling Information (17)]*.

An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake *[see Adverse Reactions (6.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

5.4 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Xgeva, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with osseous metastasis, the incidence of ONJ was higher with longer duration of exposure *[see Adverse Reactions (6.1)]*. Seventy-nine percent of patients with ONJ had a history of tooth extraction, poor oral hygiene, or use of a dental appliance as a predisposing factor. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections.

Perform an oral examination and appropriate preventive dentistry prior to the initiation of Xgeva and periodically during Xgeva therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with Xgeva. Consider temporary discontinuation of Xgeva therapy if an invasive dental procedure must be performed. There are no data available to suggest the optimal duration of treatment interruption.

Patients who are suspected of having or who develop ONJ while on Xgeva should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Clinical judgment of the treating healthcare provider should guide the management plan of each patient based on individual risk/benefit assessment.

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fracture

Atypical femoral fracture has been reported with Xgeva *[see Adverse Reactions (6.1)]*. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

During Xgeva 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 suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur

fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Xgeva therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.6 Hypercalcemia Following Treatment Discontinuation in Patients with Growing Skeletons

Clinically significant hypercalcemia has been reported in Xgeva-treated patients with growing skeletons weeks to months following treatment discontinuation. Monitor patients for signs and symptoms of hypercalcemia and treat appropriately.

5.7 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, Xgeva can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of denosumab to cynomolgus monkeys throughout pregnancy at a dose 25-fold higher than the recommended human dose of Xgeva based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth and decreased neonatal growth.

Verify the pregnancy status of females of reproductive potential prior to the initiation of Xgeva. Advise pregnant women and females of reproductive potential that exposure to Xgeva during pregnancy or within 5 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of Xgeva *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed below and elsewhere in the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.3)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.4)]*
- Hypercalcemia following treatment discontinuation in patients with growing skeletons *[see Warnings and Precautions (5.6)]*

The most common adverse reactions in patients (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (see Table 1). The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis and hypocalcemia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Bone Metastasis from Solid Tumors

The safety of Xgeva was evaluated in three randomized, double-blind, double-dummy trials *[see Clinical Trials (14.1)]* in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumors, or lytic bony lesions from multiple myeloma received at least one dose of Xgeva. In Trials 1, 2, and 3, patients were randomized to receive either 120 mg of Xgeva every 4 weeks as a subcutaneous injection or 4 mg (dose adjusted for reduced renal function) of zoledronic acid every 4 weeks by intravenous (IV) infusion. Entry criteria included serum calcium (corrected) from 8 to 11.5 mg/dL (2 to 2.9 mmol/L) and creatinine clearance 30 mL/min or greater. Patients who had received IV bisphosphonates were excluded, as were patients with prior history of ONJ or osteomyelitis of the jaw,

an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure. During the study, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

The median duration of exposure to Xgeva was 12 months (range: 0.1 - 41) and median duration on-study was 13 months (range: 0.1 - 41). Of patients who received Xgeva, 46% were female. Eighty-five percent were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range: 18 - 93). Seventy-five percent of patients who received Xgeva received concomitant chemotherapy.

Table 1. Per-patient Incidence of Selected[a] Adverse Reactions of Any Severity (Trials 1, 2, and 3)

Body System	Xgeva n = 2841 %	Zoledronic Acid n = 2836 %
GASTROINTESTINAL		
Nausea	31	32
Diarrhea	20	19
GENERAL		
Fatigue/Asthenia	45	46
INVESTIGATIONS		
Hypocalcemia[b]	18	9
Hypophosphatemia[b]	32	20
NEUROLOGICAL		
Headache	13	14
RESPIRATORY		
Dyspnea	21	18
Cough	15	15

[a] Adverse reactions reported in at least 10% of patients receiving Xgeva in Trials 1, 2, and 3, and meeting one of the following criteria:

- At least 1% greater incidence in Xgeva-treated patients, or
- Between-group difference (either direction) of less than 1% and more than 5% greater incidence in patients treated with zoledronic acid compared to placebo (US Prescribing Information for zoledronic acid)

[b] Laboratory-derived and below the central laboratory lower limit of normal [8.3 - 8.5 mg/dL (2.075 - 2.125 mmol/L) for calcium and 2.2 - 2.8 mg/dL (0.71 - 0.9 mmol/L) for phosphorus]

Severe Mineral/Electrolyte Abnormalities

- Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) occurred in 3.1% of patients treated with Xgeva and 1.3% of patients treated with zoledronic acid. Of patients who experienced severe hypocalcemia, 33% experienced 2 or more episodes of severe hypocalcemia and 16% experienced 3 or more episodes *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

- Severe hypophosphatemia (serum phosphorus less than 2 mg/dL or less than 0.6 mmol/L) occurred in 15.4% of patients treated with Xgeva and 7.4% of patients treated with zoledronic acid.

Osteonecrosis of the Jaw (ONJ)
In the primary treatment phases of Trials 1, 2, and 3, ONJ was confirmed in 1.8% of patients in the Xgeva group (median exposure of 12.0 months; range 0.1-40.5) and 1.3% of patients in the zoledronic acid group. The trials in patients with breast (Trial 1) or prostate (Trial 3) cancer included an Xgeva open label extension treatment phase where patients were offered Xgeva 120 mg once every 4 weeks (median overall exposure of 14.9 months; range 0.1-67.2). The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment, 3.7% in the second year, and 4.6% per year thereafter. The median time to ONJ was 20.6 months (range: 4-53) *[see Warnings and Precautions (5.4)]*.

In a placebo-controlled clinical trial with an extension treatment phase evaluating Xgeva for the prevention of bone metastases in patients with non-metastatic prostate cancer (a patient population for which Xgeva is not indicated), with longer treatment exposure of up to 7 years, the patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment, 3.0% in the second year, and 7.1% per year thereafter.

Atypical Subtrochanteric and Diaphyseal Fracture
Atypical femoral fracture has been reported with Xgeva *[see Warnings and Precautions (5.5)]*.

Giant Cell Tumor of Bone
The safety of Xgeva was evaluated in two single arm trials (Trials 4 and 5) *[see Clinical Trials (14.2)]* in which a total of 304 adult or skeletally mature adolescent patients with giant cell tumor of bone received at least 1 dose of Xgeva. Patients received 120 mg Xgeva subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Patients receiving concurrent bisphosphonate therapy were excluded from enrollment in both studies. Patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure were excluded from enrollment in Trial 5. During the trial, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

Of the 304 patients who received Xgeva, 145 patients were treated with Xgeva for ≥ 1 year, 44 patients for ≥ 2 years, and 15 patients for ≥ 3 years. The median number of doses received was 14 (range: 1 to 60 doses) and the median number of months on study was 11 (range: 0 to 54 months). Fifty-eight percent of the enrolled patients were women and 80% were White. The median age was 33 years (range: 13 to 83 years); a total of 10 patients were skeletally mature adolescents (13 to 17 years of age).

The adverse reaction profile of Xgeva in patients with giant cell tumor of bone was similar to that reported in Trials 1, 2, and 3. The most common adverse reactions in patients (per-patient incidence ≥ 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions were osteonecrosis of the jaw and osteomyelitis (per-patient incidence of 0.7%). The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis of the jaw (per-patient incidence of 0.7%), and tooth abscess or tooth infection (per-patient incidence of 0.7%). The adverse reaction profile appeared similar in skeletally mature adolescents and adults.

Hypocalcemia and Hypophosphatemia

- Moderate hypocalcemia (corrected serum calcium less than 8 to 7 mg/dL or less than 2 to 1.75 mmol/L) occurred in 2.6% of patients treated with Xgeva.
- Severe hypophosphatemia (serum phosphorus less than 2 to 1 mg/dL or less than 0.6 to 0.3 mmol/L) occurred in 29 patients (9.5%).

Osteonecrosis of the Jaw (ONJ)

In Trials 4 and 5, ONJ was confirmed in 4 of 304 (1.3%) patients who received Xgeva. The median time to ONJ was 16 months (range: 13 to 20 months) *[see Warnings and Precautions (5.4)]*.

Hypercalcemia of Malignancy

Xgeva was evaluated in an open-label, single-arm trial (Trial 6) in which 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy were enrolled *[see Clinical Trials (14.3)]*.

The adverse reaction profile of Xgeva in patients with hypercalcemia of malignancy was similar to that reported in Trials 1, 2, 3, 4, and 5. Adverse reactions occurring in greater than 20% of patients were nausea (30%), dyspnea (27%), decreased appetite (24%), headache (24%), peripheral edema (24%), vomiting (24%), anemia (21%), constipation (21%), and diarrhea (21%). The following adverse reactions of Grade 3 or greater severity related to study therapy were reported on study: fatigue (3%) and infection (6%). Grade 3 laboratory abnormalities included hypomagnesemia (3%), hypokalemia (3%), and hypophosphatemia (76%) of patients. No deaths on study were related to Xgeva therapy.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xgeva. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypocalcemia: Severe symptomatic hypocalcemia, including fatal cases *[see Contraindications (4.1) and Warnings and Precautions (5.3)]*.
- Hypersensitivity, including anaphylactic reactions *[see Contraindications (4.2) and Warnings and Precautions (5.2)]*.
- Musculoskeletal pain, including severe musculoskeletal pain. Positive rechallenge has been reported.

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% (7/2758) of patients with osseous metastases treated with denosumab doses ranging from 30-180 mg every 4 weeks or every 12 weeks for up to 3 years and none of the 304 patients with giant cell tumor of bone in Trials 4 and 5 tested positive for binding antibodies. No patient with positive binding antibodies tested positive for neutralizing antibodies as assessed using a chemiluminescent cell-based *in vitro* biological assay. There was no evidence of altered pharmacokinetic profile, toxicity profile, or clinical response associated with binding antibody development.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug-drug interaction trials have been conducted with Xgeva.

There was no evidence that various anticancer treatments affected denosumab systemic exposure and pharmacodynamic effect. Serum denosumab concentrations at 1 and 3 months and reductions in the bone turnover marker uNTx/Cr (urinary N-terminal telopeptide corrected for creatinine) at 3 months were similar in patients with and without prior intravenous bisphosphonate therapy and were not altered by concomitant chemotherapy and/or hormone therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, Xgeva can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are insufficient data with denosumab use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero denosumab exposure from cynomolgus monkeys dosed monthly with denosumab throughout pregnancy at a dose 25-fold higher than the recommended human dose of Xgeva based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality; and absent lymph nodes, abnormal bone growth, and decreased neonatal growth *(see Data)*.

Apprise pregnant women of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANK ligand (RANKL) expression was turned off by gene removal (a “knockout mouse”). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy starting at gestational day 20 and at a pharmacologically active dose 25-fold higher than the recommended human dose of Xgeva based on body weight, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia, and tooth malalignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels).

Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated. Mammary gland histopathology at 6 months of age was normal in female

offspring exposed to denosumab in utero; however, development and lactation have not been fully evaluated.

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.2)]*.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Xgeva (denosumab) in human milk, the effects on the breastfed infant, or the effects on milk production. Denosumab was detected in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab (≤ 0.5% milk:serum ratio) and maternal mammary gland development was normal, with no impaired lactation. However, pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.2)]*. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Xgeva treatment and any potential adverse effects on the breastfed child from Xgeva or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Based on findings in animals and its mechanism of action, Xgeva can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Xgeva treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of Xgeva.

8.4 Pediatric Use

The safety and efficacy of Xgeva have not been established in pediatric patients except in skeletally mature adolescents with giant cell tumor of bone. Xgeva is recommended only for treatment of skeletally mature adolescents with giant cell tumor of bone *[see Indications and Usage (1.2)]*.

Xgeva was studied in an open-label trial that enrolled a subset of 10 adolescent patients (aged 13-17 years) with giant cell tumor of bone who had reached skeletal maturity, defined by at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus), and had a body weight ≥ 45 kg *[see Indications and Usage (1.2) and Clinical Trials (14.2)]*. A total of two of six (33%) evaluable adolescent patients had an objective response by retrospective independent assessment of radiographic response according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. The adverse reaction profile and efficacy results appeared to be similar in skeletally mature adolescents and adults *[see Adverse Reactions (6.1) and Clinical Trials (14.2)]*.

Treatment with Xgeva may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (the target of Xgeva therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg administered once every 4 weeks, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab.

Cynomolgus monkeys exposed in utero to denosumab exhibited bone abnormalities, reduced hematopoiesis, tooth malalignment, decreased neonatal growth, and an absence of axillary, inguinal, mandibular, and mesenteric lymph nodes. Some bone abnormalities recovered once exposure was ceased following birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth *[see Use in Specific Populations (8.1)]*.

8.5 Geriatric Use

Of patients who received Xgeva in Trials 1, 2, and 3, 1260 (44%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Two clinical trials were conducted in patients without cancer and with varying degrees of renal function.

In one study, patients (N=55) with varying degrees of renal function (ranging from normal through end-stage renal disease requiring dialysis) received a single 60 mg subcutaneous dose of denosumab. In a second study, patients (N=32) with severe renal dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis) were given two 120 mg subcutaneous doses of denosumab. In both studies, greater risk of developing hypocalcemia was observed with increasing renal impairment, and with inadequate/no calcium supplementation. Hypocalcemia was mild to moderate in severity in 96% of patients. Monitor calcium levels and calcium and vitamin D intake *[see Warnings and Precautions (5.3), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no experience with overdosage of Xgeva.

11 DESCRIPTION

Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Xgeva is a sterile, preservative-free, clear, colorless to pale yellow solution.

Each single-use vial of Xgeva contains 120 mg denosumab, acetate (18 mM), polysorbate 20 (0.01%), sorbitol (4.6%), Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Xgeva binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

12.2 Pharmacodynamics

In patients with breast cancer and bone metastases, the median reduction in uNTx/Cr was 82% within 1 week following initiation of Xgeva 120 mg administered subcutaneously. In Trials 1, 2, and 3, the median reduction in uNTx/Cr from baseline to Month 3 was approximately 80% in 2075 Xgeva-treated patients.

12.3 Pharmacokinetics

Following subcutaneous administration, bioavailability was 62%. Denosumab displayed nonlinear pharmacokinetics at doses below 60 mg, but approximately dose-proportional increases in exposure at higher doses.

With multiple subcutaneous doses of 120 mg once every 4 weeks, up to 2.8-fold accumulation in serum denosumab concentrations was observed and steady state was achieved by 6 months. A mean (± standard deviation) serum steady-state trough concentration of 20.5 (± 13.5) mcg/mL was achieved by 6 months.

With the administration of subcutaneous doses of 120 mg once every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy, mean (± standard deviation) serum trough concentrations on Day 8, 15, and one month after the first dose were 19.0 (± 24.1), 31.6 (± 27.3), 36.4 (± 20.6) mcg/mL, respectively. Steady-state was achieved in 3 months after initiation of treatment with a mean serum trough concentration of 23.4 (± 12.1) mcg/mL. The mean elimination half-life was 28 days.

Special Populations

Body Weight: A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. Denosumab clearance and volume of distribution were proportional to body weight. The steady-state exposure following repeat subcutaneous administration of 120 mg every 4 weeks to 45 kg and 120 kg subjects were, respectively, 48% higher and 46% lower than exposure of the typical 66 kg subject.

Age, Gender and Race: The pharmacokinetics of denosumab was not affected by age, gender, and race.

Pediatrics: The pharmacokinetics of denosumab in pediatric patients has not been assessed.

Hepatic Impairment: No clinical trials have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.

Renal Impairment: In clinical trials of 87 patients with varying degrees of renal dysfunction, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of denosumab has not been evaluated in long-term animal studies. The genotoxic potential of denosumab has not been evaluated.

Denosumab had no effect on female fertility or male reproductive organs in monkeys at doses that were 6.5- to 25-fold higher than the recommended human dose of 120 mg subcutaneously administered once every 4 weeks, based on body weight (mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Denosumab is an inhibitor of osteoclastic bone resorption via inhibition of RANKL.

Because the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered (knockout) mice or use of other biological inhibitors of the RANK/RANKL pathway, OPG-Fc and RANK-Fc, provided additional information on the pharmacodynamic properties of denosumab. RANK/RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc also showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued.

14 CLINICAL TRIALS

14.1 Bone Metastasis from Solid Tumors

The safety and efficacy of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials comparing Xgeva with zoledronic acid. In all three trials, patients were randomized to receive 120 mg Xgeva subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE; testing for these outcome measures occurred if the main outcome measure was statistically significant. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Trial 1 enrolled 2046 patients with advanced breast cancer and bone metastasis. Randomization was stratified by a history of prior SRE (yes or no), receipt of chemotherapy within 6 weeks prior to randomization (yes or no), prior oral bisphosphonate use (yes or no), and region (Japan or other countries). Forty percent of patients had a previous SRE, 40% received chemotherapy within 6 weeks prior to randomization, 5% received prior oral bisphosphonates, and 7% were enrolled from Japan.

Median age was 57 years, 80% of patients were White, and 99% of patients were women. The median number of doses administered was 18 for denosumab and 17 for zoledronic acid.

Trial 2 enrolled 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer with bone metastasis and multiple myeloma. Randomization was stratified by previous SRE (yes or no), systemic anticancer therapy at time of randomization (yes or no), and tumor type (non-small cell lung cancer, myeloma, or other). Eighty-seven percent were receiving systemic anticancer therapy at the time of randomization, 52% had a previous SRE, 64% of patients were men, 87% were White, and the median age was 60 years. A total of 40% of patients had non-small cell lung cancer, 10% had multiple myeloma, 9% had renal cell carcinoma, and 6% had small cell lung cancer. Other tumor types each comprised less than 5% of the enrolled population. The median number of doses administered was 7 for both denosumab and zoledronic acid.

Trial 3 enrolled 1901 men with castrate-resistant prostate cancer and bone metastasis. Randomization was stratified by previous SRE, PSA level (less than 10 ng/mL or 10 ng/mL or greater) and receipt of chemotherapy within 6 weeks prior to randomization (yes or no). Twenty-six percent of patients had a previous SRE, 15% of patients had PSA less than 10 ng/mL, and 14% received chemotherapy within 6 weeks prior to randomization. Median age was 71 years and 86% of patients were White. The median number of doses administered was 13 for denosumab and 11 for zoledronic acid.

Xgeva delayed the time to first SRE following randomization as compared to zoledronic acid in patients with breast or castrate-resistant prostate cancer (CRPC) with osseous metastases (Table 2). In patients with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, Xgeva was noninferior to zoledronic acid in delaying the time to first SRE following randomization.

Overall survival and progression-free survival were similar between arms in all three trials. Mortality was higher with Xgeva in a subgroup analysis of patients with multiple myeloma (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n = 180).

Table 2. Efficacy Results for Xgeva Compared to Zoledronic Acid

	Trial 1 Metastatic Breast Cancer		Trial 2 Metastatic Solid Tumors or Multiple Myeloma		Trial 3 Metastatic CRPC[a]	
	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid
N	1026	1020	886	890	950	951
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to Bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21 (2.4)	26 (2.7)	36 (3.8)
Median Time to SRE (months)	NR[b]	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	< 0.001		< 0.001		< 0.001	
Superiority p-value[c]	0.010		0.060		0.008	
First and Subsequent SRE[d]						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority p-value [e]	0.001		0.145		0.009	

[a]CRPC = castrate-resistant prostate cancer.
[b]NR = not reached.
[c]Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid within trial.
[d]All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event.
[e]Adjusted p-values are presented.

14.2 Giant Cell Tumor of Bone

The safety and efficacy of Xgeva for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials (Trial 4 and 5) that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. Patients received 120 mg Xgeva subcutaneously every 4 weeks with additional doses on Days 8 and 15 of the first cycle of therapy.

Trial 4 was a single arm, pharmacodynamic, and proof of concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic resonance imaging (MRI) obtained within 28 days prior to study

enrollment. Patients enrolled in Trial 4 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during Xgeva treatment.

Trial 5 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Trial 5 enrolled 10 patients who were 13 - 17 years of age *[see Use in Specific Populations (8.4)]*. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease (e.g., sacral or spinal sites of disease, or pulmonary metastases); Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); Cohort 3 enrolled 11 patients who previously participated in Trial 4. Patients underwent imaging assessment of disease status at intervals determined by their treating physician.

An independent review committee evaluated objective response in 187 patients enrolled and treated in Trials 4 and 5 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Trial 4 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Trial 5). The primary efficacy outcome measure was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

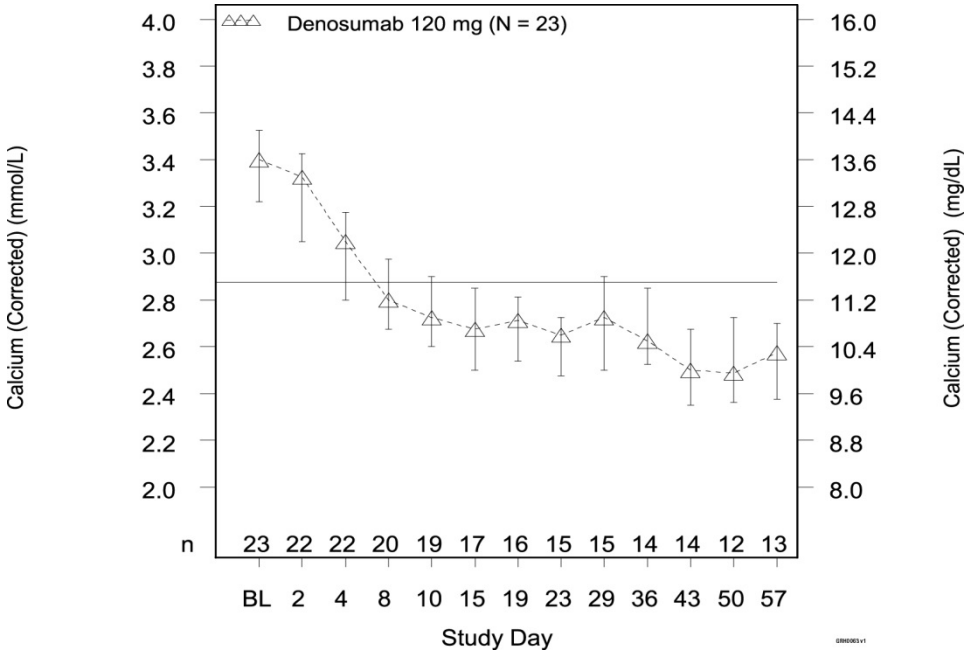
The overall objective response rate (RECIST 1.1) was 25% (95% CI: 19, 32). All responses were partial responses. The estimated median time to response was 3 months. In the 47 patients with an objective response, the median duration of follow-up was 20 months (range: 2 to 44 months), and 51% (24/47) had a duration of response lasting at least 8 months. Three patients experienced disease progression following an objective response.

14.3 Hypercalcemia of Malignancy

The safety and efficacy of Xgeva was demonstrated in an open-label, single-arm trial (Trial 6) that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy. Patients received Xgeva subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

In this trial, refractory hypercalcemia of malignancy was defined as an albumin-corrected calcium of > 12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate therapy in 7-30 days prior to initiation of Xgeva therapy. The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium (CSC) ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after Xgeva administration. Efficacy data are summarized in Figure 1 and Table 3. Concurrent chemotherapy did not appear to affect response to Xgeva.

Figure 1: Corrected Serum Calcium by Visit in Responders (Median and Interquartile Range)



N = Number of responders who received ≥ 1 dose of investigational product
n = Number of responders who had no missing data at baseline and the time point of interest

Table 3: Efficacy in Patients with Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy

	N = 33	**Proportion (%) (95% CI)**
All Responders (CSC ≤ 11.5 mg/dL) by Day 10	21	63.6 (45.1, 79.6)
All Responders by Day 57	23	69.7 (51.3, 84.4)
Complete Responders (CSC ≤ 10.8 mg/dL) by Day 10	12	36.4 (20.4, 54.9)
All Complete Responders by Day 57	21	63.6 (45.1, 79.6)

Median time to response (CSC ≤ 11.5 mg/dL) was 9 days (95% CI: 8, 19), and the median duration of response was 104 days (95% CI: 7, not estimable). Median time to complete response (CSC ≤ 10.8 mg/dL) was 23 days (95% CI: 9, 36), and the median duration of complete response was 34 days (95% CI: 1, 134).

16 HOW SUPPLIED/STORAGE AND HANDLING

Xgeva is supplied in a single-use vial.

120 mg/1.7 mL	1 vial per carton	NDC 55513-730-01

Store Xgeva in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, Xgeva must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 14 days. Discard Xgeva if not used within the 14 days. Do not use Xgeva after the expiry date printed on the label.

Protect Xgeva from direct light and heat.

Avoid vigorous shaking of Xgeva.

17 PATIENT COUNSELING INFORMATION

Drug Products with Same Active Ingredient
Advise patients that denosumab is also marketed as Prolia, and if taking Xgeva, they should not receive Prolia *[see Warnings and Precautions (5.1)]*.

Hypersensitivity
Advise patients to seek prompt medical attention if signs or symptoms of hypersensitivity reactions occur. Advise patients who have had signs or symptoms of systemic hypersensitivity reactions that they should not receive denosumab (Xgeva or Prolia) *[see Warnings and Precautions (5.2) and Contraindications (4.2)]*.

Hypocalcemia
Adequately supplement patients with calcium and vitamin D and instruct them on the importance of maintaining serum calcium levels while receiving Xgeva *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*. Advise patients to seek prompt medical attention if they develop signs or symptoms of hypocalcemia.

Osteonecrosis of the Jaw
Advise patients to maintain good oral hygiene during treatment with Xgeva and to inform their dentist prior to dental procedures that they are receiving Xgeva. Patients should avoid invasive dental procedures during treatment with Xgeva and inform their healthcare provider or dentist if they experience persistent pain and/or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.4)]*.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture
Advise patients to report new or unusual thigh, hip, or groin pain *[see Warnings and Precautions (5.5)]*.

Hypercalcemia Following Treatment Discontinuation in Patients with Growing Skeletons
Advise patients to report nausea, vomiting, headache, and decreased alertness following treatment discontinuation *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity
Advise females of reproductive potential that Xgeva can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of Xgeva *[see Use in Specific Populations (8.3)]*.

Xgeva® (denosumab)

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U.S. License No. 1080

Patent: http://pat.amgen.com/xgeva/

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