Prescription only

Prolia® Pre-filled Syringe

(denosumab)

[COMPOSITION]

[Drug Product] 1 pre-filled syringe (60 mg/1 mL) contains

Active Ingredient: denosumab (In-house) ……60 mg

Stabilizing agent: Polysorbate 20 ……0.1 mg

Excipients: Sorbitol, Glacial acetic acid, Sodium hydroxide, Water for injection, Injection needle

[APPEARANCE]

Colorless to slightly yellow, clear to slightly opalescent and practically free from particle injectable solution in colorless and clear pre-filled syringe.

[INDICATIONS]

1. Treatment of postmenopausal women with osteoporosis
2. Treatment to increase bone mass in men with osteoporosis
3. Treatment of Glucocorticoid-Induced Osteoporosis
4. Treatment of bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer
5. Treatment of bone loss in women receiving adjuvant aromatase inhibitor therapy for breast cancer

[DOSAGE AND ADMINISTRATION]

THIS DRUG should be administered by a healthcare professional.

One syringe of THIS DRUG (denosumab 60 mg) is administered as a subcutaneous injection in the upper arm, the upper thigh, or the abdomen once every 6 months.

All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily.

If a dose of THIS DRUG 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.

[PRECAUTIONS FOR USE]

1.	**Warning** Osteonecrosis of the Jaw (ONJ): ONJ has been reported in patients receiving THIS DRUG.

2. Contraindications

1) Hypocalcemia: Pre-existing hypocalcemia must be corrected prior to initiating therapy with THIS DRUG.

2) Pregnancy: THIS DRUG may cause fetal harm when administered to a pregnant woman. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with THIS DRUG.

3) Hypersensitivity: THIS DRUG is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling and urticaria.

3. Adverse Reactions

The most common (> 5% and more common than placebo) adverse reactions reported with THIS DRUG in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has also been reported in clinical trials.

The most common (> 5% and more common than placebo) adverse reactions reported with THIS DRUG in men with osteoporosis are back pain, arthralgia, and nasopharyngitis.

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

The most common (per patient incidence ≥ 10%) adverse reactions reported with THIS DRUG 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 THIS DRUG in patients with postmenopausal osteoporosis are back pain and constipation.

1) Clinical Trials Experience

① Treatment of Postmenopausal Women with Osteoporosis

The safety of THIS DRUG 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 THIS DRUG 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 THIS DRUG treatment group. The incidence of nonfatal serious adverse events was 24.2% in the placebo group and 25.0% in THIS DRUG treatment group. The percentage of patients who withdrew from the study due to adverse events was 2.1% and 2.4% for the placebo and THIS DRUG treatment groups, respectively.

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

Table 1. Adverse Reactions Occurring in ≥ 2% of Patients with Osteoporosis and More Frequently than in Placebo-treated Patients

SYSTEM ORGAN CLASS	THIS DRUG Treatment (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)

SYSTEM ORGAN CLASS	THIS DRUG Treatment (N = 3886) n (%)	Placebo (N = 3876) n (%)
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)
INFECTIONS		
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)

SYSTEM ORGAN CLASS	THIS DRUG Treatment (N = 3886) n (%)	Placebo (N = 3876) n (%)
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 THIS DRUG treatment group. The nadir in serum calcium level occurs at approximately day 10 after THIS DRUG 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 THIS DRUG 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 THIS DRUG 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 THIS DRUG treatment groups. However, the incidence of nonfatal serious infections was 3.3% in the placebo and 4.0% in THIS DRUG treatment groups. Hospitalizations due to serious infections in the abdomen (0.7% placebo vs. 0.9% THIS DRUG treatment), urinary tract (0.5% placebo vs. 0.7% THIS

DRUG treatment), and ear (0.0% placebo vs. 0.1% THIS DRUG treatment) were reported. Endocarditis was reported in no placebo patients and 3 patients receiving THIS DRUG.

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

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

Dermatologic Reactions

A significantly higher number of patients treated with THIS DRUG 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 THIS DRUG treatment groups ($p < 0.0001$). Most of these events were not specific to the injection site.

Osteonecrosis of the Jaw

ONJ has been reported in the osteoporosis clinical trial program in patients treated with THIS DRUG.

Atypical Subtrochanteric and Diaphyseal Fractures

In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with THIS DRUG. The duration of THIS DRUG exposure to time of atypical femoral fracture diagnosis was as early as 2½ years.

Multiple Vertebral Fractures (MVF) Following Discontinuation of THIS DRUG treatment

In the osteoporosis clinical trial program, multiple vertebral fractures were reported in patients after discontinuation of THIS DRUG. In the phase 3 trial in women with postmenopausal osteoporosis, 6% of women who discontinued THIS DRUG and remained in the study developed new vertebral fractures, and 3% of women who discontinued THIS DRUG and remained in the study developed new multiple vertebral fractures. The mean time to onset of multiple vertebral fractures was 17 months (range 7-43 months) after the last injection of THIS DRUG. Prior vertebral fractures was a predictor of multiple vertebral fractures after discontinuation.

Pancreatitis

Pancreatitis was reported in 4 patients (0.1%) in the placebo and 8 patients (0.2%) in THIS DRUG treatment groups. Of these reports, 1 patient in the placebo group and all 8 patients in THIS DRUG treatment group had serious events, including one death in THIS DRUG treatment 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 THIS DRUG treatment groups. New malignancies related to the breast (0.7% placebo vs. 0.9% THIS DRUG), reproductive system (0.2% placebo vs. 0.5% THIS DRUG), and gastrointestinal system (0.6% placebo vs. 0.9% THIS DRUG) were reported. A causal relationship to drug exposure has not been established.

② Treatment to Increase Bone Mass in Men with Osteoporosis

The safety of THIS DRUG 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 THIS DRUG 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 THIS DRUG treatment group. The incidence of nonfatal serious adverse events was 7.5% in the placebo group and 8.3% in THIS DRUG treatment group. The percentage of patients who withdrew from the study due to adverse events was 0% and 2.5% for the placebo and THIS DRUG treatment groups, respectively.

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

Serious Infections

Serious infection was reported in 1 patient (0.8%) in the placebo group and no patients in THIS DRUG treatment 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 THIS DRUG treatment 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 THIS DRUG treatment 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 THIS DRUG treatment group.

③ Treatment of Glucocorticoid-Induced Osteoporosis

The safety of THIS DRUG in the treatment of glucocorticoid-induced osteoporosis was assessed in the 1-year, primary analysis of a 2-year randomized, multicenter, double-blind, parallel-group, active-controlled study pf 795 patients (30% men and 70% women) aged 20 to 94 (mean age of 63 years) treated with greater than or equal to 7.5 mg/day oral prednisone (or equivalent). A total of 384 patients were exposed to 5mg daily bisphosphonate (active-control) and 394 patients were exposed to THIS DRUG administered once every 6 months as a 60mg subcutaneous dose. All patients 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 0.5% (n = 2) in the active-control group and 1.5% (n = 6) in the THIS DRUG group. The incidence of serious adverse events was 17% in the active-control group and 16% in the THIS DRUG group. The percentage of patients who withdrew from the study due to adverse events was 3.6% and 3.8% for the active-control and THIS DRUG groups, respectively.

Adverse reactions reported in ≥ 2% of patients with glucocorticoid-induced osteoporosis and more frequently with THIS DRUG than in the active-control-treated patients are shown in the table below.

Table 2. Adverse Reactions Occurring in ≥ 2% of Patients with Glucocorticoid-induced Osteoporosis and More Frequently with THIS DRUG than in Active-Control-treated Patients

Adverse Reactions	THIS DRUG (N = 394) n (%)	Oral Daily Bisphosphonate (Active-Control) (N = 384) n (%)
Back pain	18 (4.6)	17 (4.4)
Hypertension	15 (3.8)	13 (3.4)
Bronchitis	15 (3.8)	11 (2.9)

Adverse Reactions	THIS DRUG (N = 394) n (%)	Oral Daily Bisphosphonate (Active-Control) (N = 384) n (%)
Headache	14 (3.6)	7 (1.8)
Dyspepsia	12 (3.0)	10 (2.6)
Urinary tract infection	12 (3.0)	8 (2.1)
Abdominal pain upper	12 (3.0)	7 (1.8)
Upper respiratory tract infection	11 (2.8)	10 (2.6)
Constipation	11 (2.8)	6 (1.6)
Vomiting	10 (2.5)	6 (1.6)
Dizziness	9 (2.3)	8 (2.1)
Fall	8 (2.0)	7 (1.8)
Polymyalgia rheumatica*	8 (2.0)	1 (0.3)

* Events of worsening of underlying polymyalgia rheumatica

Osteonecrosis of the Jaw

No cases of ONJ were reported.

Atypical Subtrochanteric and Diaphyseal Fractures

Atypical femoral fractures were reported in 1 patients treated with THIS DRUG. The duration of THIS DRUG exposure to time of atypical femoral fracture diagnosis was 8.0 months.

Serious Infections

Serious infection was reported in 15 patients (3.9%) in the active-control group and 17 patients (4.3%) in the THIS DRUG group.

Dermatologic Reactions

Epidermal and dermal adverse events (such as dermatitis, eczema, and rashes) were reported in 16 patients (4.2%) in the active-control group and 15 patients (3.8%) in the THIS DRUG group.

④ Treatment of Bone Loss in Patients Receiving Androgen Deprivation Therapy for nonmetastatic Prostate Cancer or Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

The safety of THIS DRUG 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 THIS DRUG 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 THIS DRUG treatment group. The percentage of patients who withdrew from the study due to adverse events was 6.1% and 7.0% for the placebo and THIS DRUG treatment groups, respectively.

The safety of THIS DRUG 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 THIS DRUG 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 THIS DRUG treatment group. The percentage of patients who withdrew from the study due to adverse events was 4.2% and 0.8% for the placebo and THIS DRUG treatment groups, respectively.

Adverse reactions reported in ≥ 10% of THIS DRUG-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% THIS DRUG) and back pain (10.5% placebo vs. 11.5% THIS DRUG). Pain in extremity (7.7% placebo vs. 9.9% THIS DRUG) and musculoskeletal pain (3.8% placebo vs. 6.0% THIS DRUG) have also been reported in clinical trials. Additionally in THIS DRUG-treated men with nonmetastatic prostate cancer receiving ADT, a greater incidence of cataracts was observed (1.2% placebo vs. 4.7% THIS DRUG). Hypocalcemia (serum calcium < 8.4 mg/dL) was reported only in THIS DRUG-treated patients (2.4% vs. 0%) at the month 1 visit.

2) Postmarketing Experience

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

- 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 THIS DRUG
- Cutaneous and mucosal lichenoid drug eruptions (e.g. lichen planus-like reactions)
- Alopecia
- Hypersensitivity vasculitis
- DRESS syndrome

3) Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Less than 1% (55 out of 8113) of patients treated with THIS DRUG for up to 5 years developed antibodies for THIS DRUG. None of the patients tested positive for neutralizing antibodies. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was associated with binding antibody development.

4) Postmarketing surveillance results in Korea

As result of postmarketing surveillance conducted for re-evaluation with 3,221 patients for 6 years in Korea, incidence of adverse events is reported as 19.25% (613/3,221 patients, total 1,057 cases), regardless of causal relationship. Out of these, serious adverse reactions for which a causal relationship cannot be ruled out and unexpected adverse reactions for which a causal relationship cannot be ruled out are listed in the table below, depending on the frequency of occurrence.

		Serious adverse drug reactions 0.09% (3/3,221 patients, 4 cases)	Unexpected adverse drug reactions 0.65% (21/3,221 patients, 26 cases)
Sometimes (0.1 to less than 5%)	General disorders and administration site conditions		Pain
Rare (less than 0.1%)	Toxicosis and procedural complications		Femur fracture, spinal compression fracture
	Various gastrointestinal disorders		Diarrhea
	Infections and parasitization	Pneumonia	Periodontitis
	General disorders and administration site conditions		Pyrexia, chest pain, injection site bruising
	Injury, toxicosis and procedural complications	Spinal compression fracture	

	Musculoskeletal and connective tissue disorders		Muscle spasms, pain in jaw
	Respiratory, thoracic, and mediastinal disorders		Dyspnea
	Metabolism and nutrition disorders		Hypophagia, decreased appetite, hyperlipidemia

4. General Cautions

1) Drug Products with Same Active Ingredient

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

2) Hypersensitivity

Clinically significant hypersensitivity including anaphylaxis has been reported with THIS DRUG. 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 THIS DRUG.

3) Hypocalcemia and Mineral Metabolism

Hypocalcemia may be exacerbated by the use of THIS DRUG. Pre-existing hypocalcemia must be corrected by taking in calcium and vitamin D adequately prior to initiating therapy with THIS DRUG. 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 during treatment, especially in the first few weeks after treatment of THIS DRUG 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 THIS DRUG 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.

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 THIS DRUG. A routine oral exam should be performed by the prescriber prior to initiation of THIS DRUG treatment, and it is important to evaluate risk factors for ONJ. A dental examination with appropriate preventive dentistry is recommended prior to treatment with THIS DRUG 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 comorbid 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 THIS DRUG. 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 THIS DRUG.

Invasive dental procedures should be avoided while administrating THIS DRUG. 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 THIS DRUG should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Temporary interruption of THIS DRUG therapy should be considered in these patients whom ONJ occurred during treatment until these patients recover based on individual benefit-risk assessment.

5) Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving THIS DRUG. 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 antiresorptive 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 THIS DRUG 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 THIS DRUG therapy should be considered, pending a benefit-risk assessment, on an individual basis.

6) Multiple Vertebral Fractures (MVF) Following Discontinuation of THIS DRUG Treatment

In case of discontinuation of THIS DRUG treatment, fracture risk increases, including multiple vertebral fractures. THIS DRUG results in significant suppression of bone turnover and cessation of THIS DRUG treatment results in increased bone turnover above pretreatment values 9 months after the discontinuation, and it is reported that bone turnover then returns to pretreatment values 24 months after the discontinuation. In addition, bone mineral density returns to pretreatment values within 18 months after the discontinuation.

New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of THIS DRUG. Prior vertebral fracture was a predictor of multiple vertebral fractures after THIS DRUG discontinuation. Evaluate an individual’s benefic-risk before initiating treatment with THIS DRUG.

If THIS DRUG treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy.

7) Serious Infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in THIS DRUG treatment group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with THIS DRUG. Endocarditis was also reported more frequently in THIS DRUG-treated patients. The incidence of opportunistic infections was similar between placebo and THIS DRUG treatment 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 THIS DRUG. In patients who develop serious infections while on THIS DRUG, prescribers should assess the need for continued THIS DRUG therapy.

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 THIS DRUG treatment group compared to the placebo group. Most of these events were not specific to the injection site. Consider discontinuing THIS DRUG if severe symptoms develop.

9) Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking THIS DRUG. The time to onset of symptoms varied from one day to several months after starting THIS DRUG. Consider discontinuing use if severe symptoms develop.

10) Suppression of Bone Turnover

In clinical trials in women with postmenopausal osteoporosis, treatment with THIS DRUG resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with THIS DRUG are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with THIS DRUG may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

11) The study on the ability to drive or use of heavy machinery in patients treated with THIS DRUG have not been conducted.

5. Drug-Drug Interactions

In a study of 19 postmenopausal women with low BMD and rheumatoid arthritis treated with etanercept (50 mg subcutaneous injection once weekly), a single-dose of THIS DRUG (60 mg subcutaneous injection) was administered 7 days after the previous dose of etanercept. No clinically significant changes in the pharmacokinetics of etanercept were observed.

Cytochrome P450 substrates

In a study of 17 postmenopausal women with osteoporosis, midazolam (2 mg oral) was administered 2 weeks after a single dose of THIS DRUG (60 mg subcutaneous injection), which approximates the T_{max} of THIS DRUG. THIS DRUG did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 (CYP3A4). This indicates that THIS DRUG should not alter the pharmacokinetics of drugs metabolized by CYP3A4 in postmenopausal women with osteoporosis.

6. Use in Pregnancy and Nursing Mothers

1) Pregnancy

Risk Summary

THIS DRUG is contraindicated for use in pregnant women because it may cause harm to a fetus. There are insufficient data with THIS DRUG use in pregnant women to inform any drug-associated risks for adverse developmental outcomes. *In utero* THIS DRUG exposure from cynomolgus monkeys dosed monthly with THIS DRUG 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.

Data

Animal Data

The effects of THIS DRUG 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. In cynomolgus monkeys dosed subcutaneously with THIS DRUG 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 THIS DRUG (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 THIS DRUG *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.

The no-effect dose for THIS DRUG-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 THIS DRUG were observed (no inhibition of RANKL).

2) Lactation

Risk Summary

There is no information regarding the presence of THIS DRUG in human milk, the effects on the breastfed infant, or effects on milk production. THIS DRUG was detected in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of THIS DRUG (≤ 0.5% milk:serum ratio) and 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.

3) Females and Males of Reproductive Potential

Based on findings in animals, THIS DRUG can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating THIS DRUG 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 THIS DRUG.

Males

THIS DRUG was present at low concentrations (approximately 2% of serum exposure) in the seminal fluid of male subjects given THIS DRUG. Following vaginal intercourse, the maximum amount of THIS DRUG 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 THIS DRUG via seminal fluid.

7. Pediatric Use

THIS DRUG is not recommended in pediatric patients younger than age 4 years because of the high rates of skeletal growth and the potential for THIS DRUG to negatively affect long-bone growth and dentition. The safety and effectiveness of THIS DRUG in pediatric patients have not been established.

Treatment with THIS DRUG 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 THIS DRUG 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 THIS DRUG.

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.

8. Geriatric Use

No dose adjustment is necessary in Geriatric Use.
Of the total number of patients in clinical studies of THIS DRUG, 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. Of the patients in the glucocorticoid-induced osteoporosis study, 355 patients (47%) were ≥ 65 years old, while 132 patients (17%) 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.

9. 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 THIS DRUG 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.

10. Hepatic Impairment

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

11. Overdosage

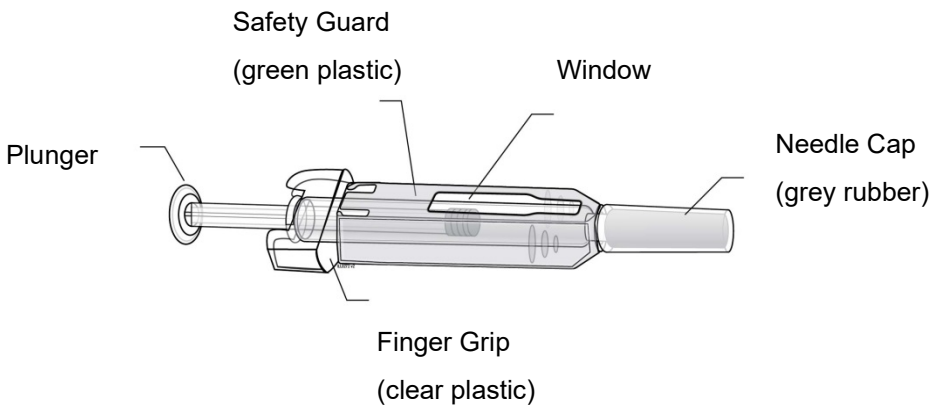
There is no experience with overdosage with THIS DRUG. In clinical trials, the drug has been administered to 180 mg every 4 weeks (cumulated dose up to 1080 mg over 6 months).

12. Cautions in Administration

1) Visually inspect THIS DRUG for particulate matter and discoloration prior to administration whenever solution and container permit. THIS DRUG 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.
2) People sensitive to latex should not handle the grey needle cap on the single-dose prefilled syringe, which contains dry natural rubber (a derivative of latex).
3) Prior to administration, THIS DRUG may be removed from the refrigerator and brought to room temperature (up to 25°C) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm THIS DRUG in any other way.
4) Instructions for Prefilled Syringe with Needle Safety Guard

IMPORTANT: In order to minimize accidental needlesticks, THIS DRUG will have a green safety guard.

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

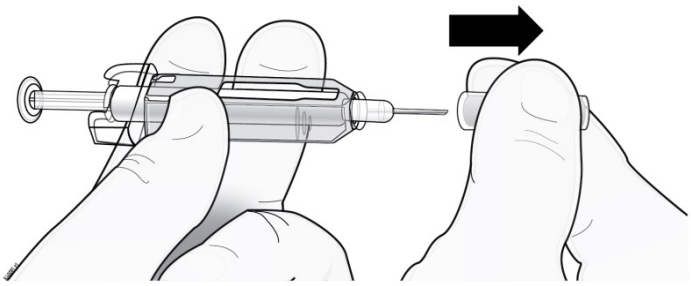


Activate the green safety guard manually (slide over the needle) after the injection.

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

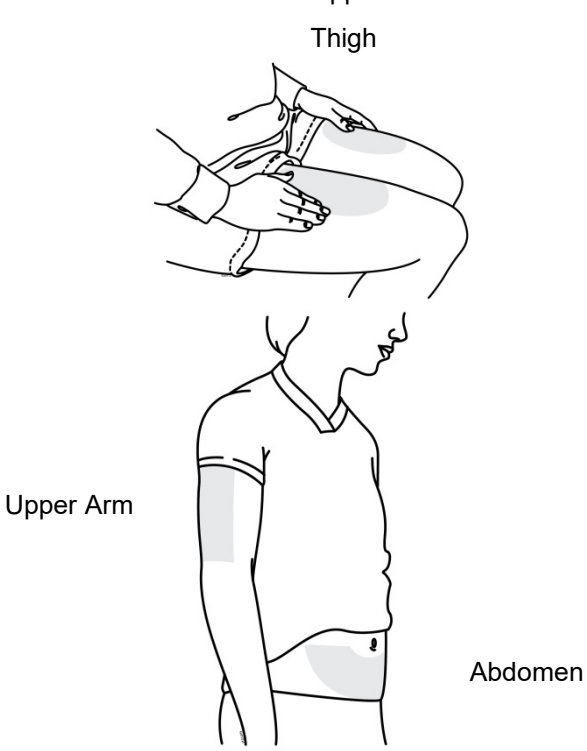
① Step 1: Remove Grey Needle Cap

Remove needle cap.

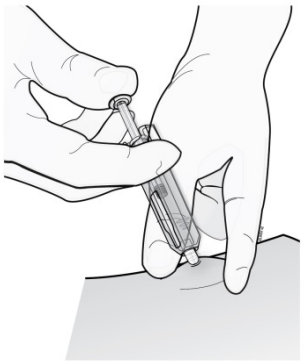


② Step 2: Administer Subcutaneous Injection

Choose an injection site. The recommended injection sites for THIS DRUG 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.



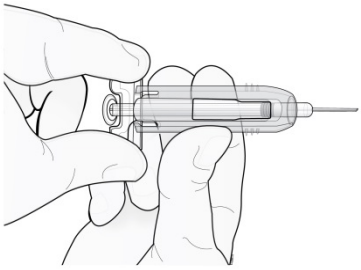
DO NOT put grey needle cap back on needle.

③ Step 3: Immediately Slide Green Safety Guard Over Needle

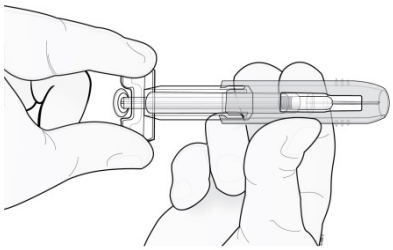
With the *needle pointing away from you.*

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 too firmly when sliding green safety guard over needle – 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.

13. Cautions for Storage and Handling

1) Store THIS DRUG in a refrigerator at 2°C to 8°C in the original carton. Do not freeze. Prior to administration, THIS DRUG may be allowed to reach room temperature (up to 25°C) in the original container.
2) Once removed from the refrigerator, THIS DRUG must not be exposed to temperatures above 25°C and must be used within 14 days. If not used within the 14 days, THIS DRUG should be discarded. Do not use THIS DRUG after the expiry date printed on the label.
3) Protect THIS DRUG from direct light and heat.
4) Avoid vigorous shaking of THIS DRUG.

[STORAGE CONDITION]

Hermetic container, do not freeze and store in refrigerator (2~8°C), protect from the light

[PACKAGING UNIT]

1 X pre-filled syringe (1 mL)/Box

[EXPIRY DATE]

Refer to the outer package (YY/MM/DD)

[PRODUCT LICENSE HOLDER]

Amgen Inc.

One Amgen Center Drive, Thousand Oaks, CA 91320, USA

[MANUFACTURER]

1) Drug Substance

Amgen Singapore Manufacturing Pte. Ltd (ASM)

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2) Drug Product, Packaging and Labeling

Amgen Manufacturing Limited (AML)

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- If products are decomposed, deteriorated, damaged, contaminated or expired, they can be exchanged at the pharmacy, clinic, hospital, or wholesaler where purchased. Please contact the facility where you bought the product for return or exchange.
- You will be compensated for consumers' damages as per the Consumer Injury Compensation Rule.
- Relief of injury from adverse drug reaction: Korea Institute of Drug Safety & Risk Management (Tel: 1644-6223, www.drugsafe.or.kr)
- You can find the latest product information after the following revision date on the MFDS medicines integrated information system (http://nedrug.mfds.go.kr) or the Amgen Korea Limited website (www.amgen.co.kr).
- Amgen Korea Limited contact phone : 00798 611 3554 (toll free) / 02-3434-4899 / medinfo.JAPAC@amgen.com

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