Prolia®
denosumab

NAME OF THE MEDICINAL PRODUCT

Prolia 60 mg solution for injection in pre-filled syringe

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 60 mg of denosumab in 1.0 mL solution (60 mg/mL).

Denosumab has an approximate molecular weight of 147 kDa. Denosumab is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

PHARMACEUTICAL FORM

Solution for subcutaneous injection.

Clear, colourless to slightly yellow solution, pH 5.2 and may contain trace amounts of translucent to white proteinaceous particles.

CLINICAL PARTICULARS

Indications

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 of fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.

Treatment of men with osteoporosis at high risk of fracture
Prolia is indicated for the treatment of men with osteoporosis at high risk of fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other osteoporosis therapy.

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.

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 nonmetastatic breast cancer.

Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see Clinical Studies)

Dosage and Administration

Administration
Administration should be performed by an individual who has been adequately trained in injection techniques.

Dosage
The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months.

All patients should receive calcium 1,000 mg daily and at least 400 IU vitamin D daily whilst undergoing treatment.

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.

Populations

Children
Prolia is not indicated for use in paediatric patients. In clinical trials, hypercalcemia has been reported very commonly in paediatric patients with osteogenesis imperfecta treated with denosumab. Some cases required hospitalisation and were complicated by acute renal injury (see Warnings and Precautions). In animal studies, inhibition of RANK/RANK ligand (RANKL) with a construct of osteoprotegerin bound to Fc (OPG-Fc) has been coupled to inhibition of bone growth and lack of tooth eruption (see Pre-Clinical Safety Data). Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

Elderly
Based on the available safety and efficacy data in the elderly, no dosage adjustment is required (see Pharmacokinetics: Special Patient Populations).

Renal Impairment
Based on the available safety and efficacy data in the elderly, no dosage adjustment is required in patients with renal impairment (see Pharmacokinetics: Special Patient Populations).

No data is available in patients with long-term systemic glucocorticoid therapy and severe renal impairment (GFR < 30 mL/min).

Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis.

Hepatic Impairment
The safety and efficacy of Prolia have not been studied in patients with hepatic impairment.

Contraindications

Hypocalcaemia.

Clinically significant hypersensitivity to denosumab or any components of Prolia.

Warnings and Precautions

Adequate intake of supplemental calcium and vitamin D is important in all patients receiving Prolia.

Pre-existing hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. In patients predisposed to hypocalcaemia, clinical monitoring of calcium levels is recommended during treatment, especially in the first few weeks of initiating therapy (see Adverse Reactions). Hypocalcaemia following Prolia administration is a significant risk in patients with severe renal impairment (creatinine clearance < 30 mL/min), or receiving dialysis. Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcaemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation.

In a clinical trial of over 7,800 women with postmenopausal osteoporosis, serious infections leading to hospitalisation were reported more frequently in the Prolia group than in the placebo group (see Adverse Reactions). 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 subjects. The incidence of opportunistic infections was balanced 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.

In a large clinical trial of over 7,800 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). Consider discontinuing Prolia if severe symptoms develop.

Osteonecrosis of the Jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. Cases of osteonecrosis of the jaw (ONJ) were reported predominantly in patients with advanced cancer receiving 120 mg every 4 weeks. ONJ was reported rarely in patients with osteoporosis receiving 60 mg every 6 months (see Adverse Reactions). Poor oral hygiene and invasive dental procedures (e.g., tooth extraction) were risk factors for ONJ in patients receiving Prolia in clinical trials. The risk of ONJ may increase with duration of exposure to Prolia. It is important to evaluate patients for risk of ONJ before starting treatment. If risk factors are identified, a dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia. Risk factors for ONJ include invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anaemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment with Prolia.

Avoid invasive dental procedures during treatment with Prolia. For patients in whom invasive dental procedures cannot be avoided, the clinical judgment of the treating physician 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 oral surgeon. In patients who develop ONJ during treatment with Prolia, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.

Atypical femoral fractures have been reported in patients receiving Prolia. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur and may be bilateral. Specific radiographic findings characterise these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthiritis, hypophosphatasia), and with use of certain pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture, and the contralateral femur should also be examined.

In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodelling as evidenced by markers of bone turnover and bone histomorphometry. 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 remodelling 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.

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

Multiple vertebral fractures (MVF) may occur following discontinuation of treatment with Prolia, particularly in patients with a history of vertebral fracture. Advise patients not to interrupt Prolia therapy without their physician's advice. Evaluate the individual benefit/risk before discontinuing treatment with Prolia. If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy.

Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

Prolia is not indicated for use in paediatric patients. In clinical trials, hypercalcemia has been reported in paediatric patients with osteogenesis imperfecta treated with denosumab. Some cases required hospitalisation (see Dosage and Administration: Populations).

Interactions

Prolia (60 mg subcutaneously) did not affect the pharmacokinetics of midazolam, a drug metabolised by cytochrome P450 3A4 (CYP3A4).

Pregnancy and Lactation

Pregnancy
There is no adequate data in pregnant women. Prolia is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with Prolia.

At AUC exposures up to 100-fold higher than the human exposure (60 mg every 6 months), denosumab showed no evidence of impaired fertility in cynomolgus monkeys.

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (60 mg every 6 months), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined.

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months), there were increased stillbirths; and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

Studies in knockout mice suggest absence of RANKL could interfere with the development of lymph nodes in the foetus and may impair postnatal dentition and bone growth; and may also interfere with maturation of the maternal mammary gland leading to impaired lactation postpartum.

Lactation
It is not known if denosumab is excreted in human milk. Because denosumab has the potential to cause adverse reactions in breast-feeding infants, a decision should be made whether to discontinue breast-feeding or discontinue the medicinal product.

Effects on Ability to Drive and Use Machines

No studies on the effect on the ability to drive or use heavy machinery have been performed in patients receiving denosumab.

Adverse Reactions

The most common adverse reactions reported with Prolia are back pain, pain in extremity, musculoskeletal pain, hypercholesterolaemia and cystitis.

The most common adverse reactions leading to discontinuation of Prolia are back pain and constipation.

The following convention has been used for the classification of the adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness. Within each frequency grouping and system organ class, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	Frequency category	Undesirable effect
Infections and infestations	Uncommon	Cellulitis
Metabolism and nutrition disorders	Rare	Hypocalcaemia[1]
Skin and subcutaneous tissue disorders	Common Common Uncommon	Eczema[2] Alopecia Lichenoid drug eruptions
	Very Rare	Hypersensitivity vasculitis
	Not Known	Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Musculoskeletal and connective tissue disorders	Very Common Rare Rare Uncommon Not Known	Pain in extremity Osteonecrosis of the jaw[1,4] Atypical femoral fractures[1,3] Multiple vertebral fractures[5] Osteonecrosis of the external auditory canal[1]

[1] See Warnings and Precautions
[2] Includes dermatitis, allergic dermatitis, atopic dermatitis and contact dermatitis
[3] In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with Prolia
[4] In the osteoporosis clinical trial program, ONJ were reported rarely in patients treated with Prolia
[5] In the osteoporosis clinical trial program, MVF were reported in patients following discontinuation of treatment with Prolia, particularly in those with a history of vertebral fracture.

Postmarketing Data

Hypersensitivity Reactions
Hypersensitivity reactions, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving Prolia.

Severe Hypocalcaemia
Severe symptomatic hypocalcaemia has been reported in patients at increased risk of hypocalcaemia receiving Prolia.

Musculoskeletal Pain
Musculoskeletal pain, including severe cases, has been reported in patients receiving Prolia.

Lichenoid drug eruptions
Lichenoid drug eruptions (e.g. lichen planus-like reactions), have been reported in patients in the post-marketing setting.

Overdose
No data from clinical trials are available regarding overdosage of Prolia.

Denosumab has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1,080 mg over 6 months), and no additional adverse effects were observed.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action
Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors, independent of bone surface. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival. Denosumab therefore reduces bone resorption and increases bone mass and strength in both cortical and trabecular bone.

Pharmacodynamic effects
In clinical studies, treatment with 60 mg of denosumab resulted in rapid reduction in the bone resorption marker serum type 1 C-telopeptides (CTX) within 6 hours of subcutaneous administration (by approximately 70%) with reductions of approximately 85% occurring by 3 days. CTX reductions were maintained over the 6-months dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to approximately ≥ 45% (range 45-80%), reflecting the reversibility of denosumab's effects on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Consistent with the physiological coupling of bone formation and resorption in skeletal remodelling, reductions in bone formation markers (e.g., bone specific alkaline phosphatase [BSAP] and serum N-terminal propeptide of type I collagen [P1NP]) were observed beginning 1 month after the first dose of denosumab.

Bone turnover markers (bone resorption and formation markers) generally reached pre-treatment levels within 9 months after the last 60 mg subcutaneous dose. Upon re-initiation, the degree of inhibition of CTX by denosumab was similar to that observed in patients initiating denosumab treatment.

In a clinical study of postmenopausal women with low bone mass (N = 504) who were previously treated with alendronate for a median duration of 3 years, those transitioning to receive denosumab experienced additional reductions in serum CTX, compared with women who remained on alendronate. In this study the changes in serum calcium were similar between the two groups.

Immunogenicity
Denosumab is a human monoclonal antibody; as with all therapeutic proteins, there is a theoretical potential for immunogenicity. More than 13,000 patients were screened for binding antibodies using a sensitive electrochemiluminescent bridging immunoassay. Less than 1% of patients treated with denosumab for up to 5 years tested positive (including pre-existing, transient, and developing antibodies). The patients that tested positive for binding antibodies were further evaluated for neutralising antibodies using a chemiluminescent cell-based *in vitro* biological assay and none of them tested positive. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was associated with binding antibody development.

PHARMACOKINETICS
Following subcutaneous administration, denosumab displayed non-linear pharmacokinetics with dose over a wide dose range, and dose-proportional increases in exposure for doses of 60 mg (or 1 mg/kg) and higher.

Absorption
Following a 60 mg subcutaneous dose of denosumab, bioavailability was 61% and maximum serum denosumab concentrations (C_{max}) of 6 μg/mL (range 1-17 μg/mL) occurred in 10 days (range 2-28 days). After C_{max}, serum levels declined with a half-life of 26 days (range 6-52 days) over a period of 3 months (range 1.5-4.5 months). Fifty-three percent of patients had no measurable amounts of denosumab detected at 6 months post-dose.

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

Metabolism
Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin. Based on nonclinical data, denosumab metabolism is expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination
Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is not expected to be eliminated via hepatic metabolic mechanisms (e.g., cytochrome P450 [CYP] enzymes). Based on nonclinical data, its elimination is expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Drug Interactions

In a study of 17 postmenopausal women with osteoporosis, midazolam (2 mg oral) was administered two weeks after a single dose of denosumab (60 mg subcutaneously), which corresponds to time of maximal pharmacodynamic effects of denosumab. Denosumab did not affect the pharmacokinetics of midazolam, which is metabolised by cytochrome P450 3A4 (CYP3A4).

Special Patient Populations

Elderly (greater than or equal to 65 years of age)
Age was not found to be a significant factor on denosumab pharmacokinetics in a population pharmacokinetic analysis of patients ranging in age from 28 to 87 years of age.

Children and Adolescents (up to 18 years of age)
No pharmacokinetic data are available in paediatric patients.

Race
The pharmacokinetics of denosumab were not affected by race in postmenopausal women or in breast cancer patients undergoing hormone ablation.

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 and pharmacodynamics of denosumab; therefore 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.

CLINICAL STUDIES

Treatment of Postmenopausal Osteoporosis
The efficacy and safety of denosumab in the treatment of postmenopausal osteoporosis was demonstrated in FREEDOM, a 3-year, randomised, double-blind, placebo-controlled, multinational study that demonstrated that denosumab was effective compared to placebo in reducing new vertebral, nonvertebral and hip fractures in postmenopausal women with osteoporosis.

7,808 women aged 60-91 years were enrolled of which 23.6% had prevalent vertebral fractures.

Women were randomised to receive subcutaneous injections of either placebo (N = 3,906) or denosumab 60 mg (N = 3,902) once every 6 months. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily. The primary efficacy variable was the incidence of new vertebral fractures. Secondary efficacy variables included the incidence of nonvertebral fractures and hip fractures, assessed at 3 years.

Denosumab significantly reduced the risk of new vertebral, nonvertebral, and hip fractures compared with placebo. All 3 efficacy fracture endpoints achieved the statistical significance level based on the pre-specified sequential testing scheme.

Effect on vertebral fractures
Denosumab significantly reduced the risk of new vertebral fractures (primary endpoint) by 68% (risk ratio: 0.32; $p < 0.0001$) over 3 years. The 3-year fracture rates for new vertebral fractures were 7.2% in the placebo group and 2.3% in the Prolia group (unadjusted absolute risk reduction of 4.8%). Reductions were also observed over 1 year (61% relative risk reduction; 1.4% unadjusted absolute risk reduction) and 2 years (71% relative risk reduction; 3.5% unadjusted absolute risk reduction) (all $p < 0.0001$).

Denosumab also reduced the risk of other pre-specified categories of fractures, including new and worsening vertebral fractures (67% relative risk reduction, 4.8% unadjusted absolute risk reduction), multiple new vertebral fractures (61% relative risk reduction, 1.0% unadjusted absolute risk reduction), clinical vertebral fractures (69% relative risk reduction, 1.8% unadjusted absolute risk reduction) over 3 years.

The reductions in the risk of new vertebral fractures by denosumab over 3 years were consistent and significant regardless of 10-year major osteoporotic baseline fracture risk as assessed by FRAX® (WHO's Fracture Risk Assessment Tool algorithm) and whether or not women had a prevalent vertebral fracture or history of a nonvertebral fracture, and regardless of baseline age, BMD, bone turnover level and prior use of a medicinal product for osteoporosis.

In postmenopausal women with osteoporosis over the age of 75, denosumab reduced the incidence of new vertebral (64%), and nonvertebral (16%) fractures.

Effect on all clinical fractures
Denosumab significantly decreased the risk of nonvertebral fractures (secondary endpoint) by 20% (hazard ratio: 0.80; p = 0.0106) over 3 years. Three-year nonvertebral fracture rates were 8.0% in the placebo group to 6.5% in the denosumab group (unadjusted absolute risk reduction of 1.5%).

Denosumab also reduced the risk of clinical (30% relative risk reduction, 2.9% unadjusted absolute risk reduction), major nonvertebral (20% relative risk reduction, 1.2% unadjusted absolute risk reduction), and major osteoporotic fractures (35% relative risk reduction, 2.7% unadjusted absolute risk reduction) over 3 years.

In women with baseline femoral neck BMD T-score ≤ -2.5, denosumab reduced the incidence of nonvertebral fractures (35% relative risk reduction, 4.1% unadjusted absolute risk reduction, p < 0.001) over 3 years. Reductions in nonvertebral fractures were observed regardless of baseline 10-year probability of a major osteoporotic fracture as assessed by FRAX®.

Effect on hip fractures
Denosumab significantly decreased the risk of hip fractures (secondary endpoint) by 40% (hazard ratio: 0.60; p = 0.0362) over 3 years. Three-year hip fracture rates were 1.2% in the placebo group and 0.7% in the denosumab group (unadjusted absolute risk reduction of 0.5%). The reductions in the risk of hip fractures over 3 years were consistent and significant regardless of baseline 10-year probability of a hip fracture as assessed by FRAX®.

In women with high fracture risk as defined above by baseline age, BMD and prevalent vertebral fracture, a 48% relative risk reduction was observed with denosumab (1.1% unadjusted absolute risk reduction).

In a post-hoc analysis in postmenopausal women with osteoporosis over the age of 75 denosumab reduced the incidence of hip fractures (62%).

Effect on bone mineral density (BMD)
Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 1, 2 and 3 years. Denosumab increased BMD by 9.2% at the lumbar spine, 6.0% at the total hip, 4.8% at the femoral neck, 7.9% at the hip trochanter, 3.5% at the distal 1/3 radius and 4.1% at the total body over 3 years. Increases in BMD at lumbar spine, total hip and hip trochanter were observed as early as 1 month after the initial dose. Denosumab increased lumbar spine BMD from baseline in 96% of postmenopausal women at 3 years. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, weight/BMI, BMD and bone turnover level.

Bone Histology
Histology assessments showed bone of normal architecture and quality, as well as the expected decrease in bone turnover relative to placebo treatment. There was no evidence of mineralisation defects, woven bone or marrow fibrosis.

Open-label Extension Study in the Treatment of Postmenopausal Osteoporosis
A total of 4,550 women who missed no more than one dose of Prolia in the FREEDOM study (N = 7,808) and completed the month 36 study visit enrolled in a 7-year, multinational, multicenter, open label, single-arm extension study to evaluate the long-term safety and efficacy of Prolia. All women in the extension study were to receive Prolia every 6 months as a single 60 mg SC dose, as well as daily calcium (at least 1 g) and vitamin D (at least 400 IU).

Based on data through 7 years of the extension, in the long-term group, Prolia treatment maintained a low incidence of new vertebral and non-vertebral fractures (7.0% of women had at least one new vertebral fracture; 9.3% of women had at least one nonvertebral fracture).

Table 1. The Effect of Prolia on the Yearly Incidence of New Vertebral and Nonvertebral Fractures Through 7 Years of the Extension Study

	Long-term Prolia Group[a]			**Cross-over Prolia Group**[b]	
Exposure to Prolia	**Proportion of Women with New Vertebral Fractures (%)**[c]	**Proportion of Women with Nonvertebral Fractures (%)**[d]	**Exposure to Prolia**	**Proportion of Women with New Vertebral Fractures (%)**[c]	**Proportion of Women with Nonvertebral Fractures (%)**[d]
Year 4	1.5[e] (N = 2116)	1.5 (N = 2343)	**Year 1**	0.9[e] (N = 1991)	2.5 (N = 2207)
Year 5		1.2 (N = 2244)	**Year 2**		2.0 (N = 2105)
Year 6	1.2 (N = 1809)	1.8 (N = 2067)	**Year 3**	1.5 (N = 1695)	2.6 (N = 1965)
Year 7	1.4[e] (N = 1585)	1.6 (N = 1867)	**Year 4**	1.9[e] (N = 1508)	1.2 (N = 1756)
Year 8		0.8 (N = 1743)	**Year 5**		1.8 (N = 1646)
Year 9	1.3[e] (N = 1323)	1.1 (N = 1585)	**Year 6**	1.6 (N = 1267)	1.5 (N = 1515)
Year 10		1.9 (N = 1451)	**Year 7**		1.7 (N = 1394)

[a] Long-term group: women who received Prolia in the FREEDOM study and continued on therapy in the extension
[b] Cross-over group: women who received placebo in the FREEDOM study and transitioned to Prolia in the extension
[c] Based on crude incidence
[d] Based on Kaplan-Meier estimate
[e] Annualized yearly subject incidence

In the long-term group, Prolia treatment continued to increase BMD from the extension baseline through 7 years at the lumbar spine (10.8%), total hip (3.4%), femoral neck (3.8%), and trochanter (5.1%). Percent increase in BMD from the original FREEDOM Study baseline (ie, after 10 years of treatment) was 21.7% at the lumbar spine, 9.2% at the total hip, 9.0% at the femoral neck, and 13.0% at the trochanter.

In the cross-over group, Prolia initiation was associated with increases in BMD from the extension baseline through 7 years at the lumbar spine (16.5%), total hip (7.4%), femoral neck (7.1%), and trochanter (10.3%).

Comparative Clinical Data vs alendronate in the Treatment of Postmenopausal Women with Low Bone Mass
In two randomised, double-blind, active-controlled studies, one in treatment-naïve women and another in women previously treated with alendronate, denosumab showed significantly greater increases in BMD and reductions in bone turnover markers (e.g., serum CTX), compared to alendronate.

Consistently greater increases in BMD were seen at the lumbar spine, total hip, femoral neck, hip trochanter, and distal 1/3 radius in women treated with denosumab, compared to those who continued to receive alendronate therapy (all $p < 0.05$).

Treatment of Osteoporosis in Men

The efficacy and safety of Prolia in the treatment of men with osteoporosis was demonstrated in a 1-year, randomised, double-blind, placebo-controlled, multinational study of men with low bone mass, who 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 and with history of prior fragility fracture were also enrolled. Men with other diseases (such as rheumatoid arthritis, osteogenesis impefecta, 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 and were randomised to receive SC injections of either placebo (n = 121) or Prolia 60 mg (n = 121) once every 6 months. Patients also received at least 1,000 mg calcium and at least 800 IU vitamin D supplementation daily.

The primary efficacy variable was percent change in lumbar spine BMD at 1 year. Secondary efficacy variables included percent change in total hip, hip trochanter, femoral neck, and distal 1/3 radius BMD at 1 year, and change in CTX at day 15.

Treatment with Prolia significantly increased BMD from baseline at the lumbar spine and all measured skeletal sites (proximal femur, distal radius) at 1 year. Prolia increased lumbar spine BMD by 4.8%, total hip BMD by 2.0%, hip trochanter by 2.3%, femoral neck BMD by 2.2%, distal 1/3 radius BMD by 0.9%, relative to placebo.

Increases in BMD at lumbar spine, total hip, and hip trochanter were observed as early as 6 months. Prolia increased lumbar spine BMD from baseline in 94.7% of men at 1 year.

Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, weight/body mass index (BMI), BMD, 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). Qualitative histology assessments showed normal architecture and quality with no evidence of mineralisation defects, woven bone, or marrow fibrosis in patients treated with Prolia.

Treatment of bone loss associated with systemic glucocorticoid therapy

Efficacy and safety of Prolia in the treatment of bone loss associated with systemic glucocorticoid therapy were investigated in the 12-month primary analysis of a 2-year, randomised, multicentre, double-blind, double-dummy, parallel-group, active-controlled study of 795 patients (70% women and 30% men) aged 20 to 94 years treated with ≥ 7.5 mg daily oral prednisone (or equivalent) for an expected duration of 6 months or longer.

Two subpopulations were studied: glucocorticoid-continuing (≥ 7.5 mg daily prednisone or its equivalent for ≥ 3 months prior to study enrolment; n = 505) and glucocorticoid-initiating (≥ 7.5 mg daily prednisone or its equivalent for < 3 months prior to study enrolment; n = 290). Patients were randomised (1:1) to receive either Prolia 60 mg subcutaneously once every 6 months or oral risedronate 5 mg once daily

(active control) for 2 years. Patients received calcium (at least 1,000 mg) and vitamin D (at least 800 IU) supplementation daily.

Enrolled patients < 50 years of age were required to have a history of osteoporotic fracture. Enrolled patients ≥ 50 years of age who were in the glucocorticoid-continuing subpopulation were required to have a baseline BMD T-score of ≤ −2.0 at the lumbar spine, total hip, or femoral neck; or a BMD T-score ≤ −1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture.

Effect on Bone Mineral Density (BMD)
In the glucocorticoid-continuing subpopulation, Prolia demonstrated a greater increase in lumbar spine BMD compared to risedronate at 1 year (Prolia 3.6%, risedronate 2.0%; $p < 0.001$) and 2 years (Prolia 4.5%, risedronate 2.2%; $p < 0.001$). In the glucocorticoid-initiating subpopulation, Prolia demonstrated a greater increase in lumbar spine BMD compared to risedronate at 1 year (Prolia 3.1%, risedronate 0.8%; $p < 0.001$) and 2 years (Prolia 4.6%, risedronate 1.5%; $p < 0.001$).

In addition, Prolia demonstrated a significantly greater mean percent increase in BMD from baseline compared to risedronate at the total hip, femoral neck, and hip trochanter.

The study was not powered to show a difference in fractures. At 1 year, the subject incidence of new radiological vertebral fracture was 2.7% (denosumab) versus 3.2% (risedronate). The subject incidence of non-vertebral fracture was 4.3% (denosumab) versus 2.5% (risedronate). At 2 years, the corresponding numbers were 4.1% versus 5.8% for new radiological vertebral fractures and 5.3% versus 3.8% for non-vertebral fractures. Most of the fractures occurred in the GC-C subpopulation.

Clinical efficacy in the treatment of bone loss associated with hormone ablation

Treatment of bone loss in men at high risk of fracture undergoing androgen deprivation therapy for prostate cancer
The efficacy and safety of denosumab in the treatment of bone loss associated with androgen deprivation was assessed in a 3-year randomised, double-blind, placebo-controlled, multinational study of 1,468 men with non-metastatic prostate cancer aged 48-97 years. Men less than 70 years of age also had either a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 or a history of an osteoporotic fracture. Subjects either received subcutaneous injections of either denosumab 60 mg (N = 734) or placebo (N = 734) once every 6 months. Men received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

Significant increases in BMD were observed at the lumbar spine, total hip, femoral neck and the hip trochanter as early as 1 month after the initial dose. Denosumab increased lumbar spine BMD by 7.9%, total hip BMD by 5.7%, femoral neck BMD by 4.9%, hip trochanter BMD by 6.9%, distal 1/3 radius BMD by 6.9%, and total body BMD by 4.7% over 3 years, relative to placebo ($p < 0.0001$). Consistent effects on BMD were observed at the lumbar spine regardless of age, race, geographical region, weight/BMI, BMD, bone turnover level; duration of androgen deprivation and presence of vertebral fracture at baseline.

Denosumab significantly decreased the risk of new vertebral fractures by 62% (hazard ratio: 0.38; $p < 0.0063$) over 3 years. Reductions were also observed over 1 year (85% relative risk reduction 1.6% absolute risk reduction), and 2 years (69% relative risk reduction; 2.2% absolute risk reduction) (all $p < 0.01$).

Treatment of bone loss in women at high risk of fracture undergoing aromatase inhibitor therapy for breast cancer

The efficacy and safety of denosumab in the treatment of bone loss associated with adjuvant aromatase inhibitor therapy was assessed in a 2-year, randomised, double-blind, placebo-controlled multinational study of 252 women with non-metastatic breast cancer aged 35-84 years. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip or femoral neck. Women were randomised to receive subcutaneous injections of either denosumab 60 mg (n = 127) or placebo (n = 125) once every 6 months. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily. The primary efficacy variable was percent change in lumbar spine BMD; fracture efficacy was not evaluated.

Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 2 years: 7.6% at the lumbar spine, 4.7% at the total hip, 3.6% at the femoral neck, 5.9% at the hip trochanter, 6.1% at the distal 1/3 radius and 4.2% at the total body. Significant increases in BMD were observed at the lumbar spine as early as 1 month after the initial dose. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, duration of aromastase inhibitor therapy, weight/BMI, prior chemotherapy, prior selective estrogen receptor modulator (SERM) use and time since menopause.

Pre-Clinical Safety Data

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.

Reproductive toxicology

Fertility

Denosumab had no effect on female fertility or male reproductive organs in monkeys at AUC exposures that were 100- to 150-fold higher than the human exposure at 60 mg administered subcutaneously once every 6 months.

Animal Pharmacology

Long-term treatment (16 months) of aged ovariectomised monkeys with denosumab at doses of 25 or 50 mg/kg SC once monthly was associated with significant gains in the mass, density (BMD), and strength of cancellous and cortical bone. Bone tissue was normal with no evidence of mineralisation defects, accumulation of osteoid or woven bone.

Transition from 6-months treatment with alendronate to 25 mg/kg denosumab in ovariectomised monkeys did not cause any meaningful decreases of serum calcium. Bone strength and reduction in bone resorption at all skeletal sites were maintained or improved.

Abnormal growth plates were observed in adolescent monkeys dosed with denosumab at 10 and 50 mg/kg SC (27 and 150 times the AUC exposure in adult humans dosed with denosumab at 60 mg SC every 6 months), consistent with the pharmacological actvity of denosumab.

In a study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months), there was increased post-natal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth to 6 months of age, the effects on bone returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralisation in multiple tissues was seen in one recovery animal. Maternal mammary gland development was normal.

Additional information on the pharmacodynamic properties of denosumab has been obtained from knockout mice lacking RANK or RANKL, and by the use of inhibitors of the RANKL pathway in rodents such as OPG-Fc. Knockout mice: (1) had an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy); (2) exhibited impairment of lymph node formation; and (3) exhibited reduced bone growth and lack of tooth eruption. Similar phenotypic changes were seen in a corroborative study in 2-week old rats given OPG-Fc. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued.

Tissue distribution studies indicated that denosumab does not bind to tissues known for expression of other members of the TNF superfamily, including TNF-related apoptosis-inducing ligand (TRAIL).

PHARMACEUTICAL PARTICULARS

List of Excipients

Glacial acetic acid*
Sodium hydroxide*
Sorbitol
Polysorbate 20
Water for Injection
* Acetate buffer is formed by mixing acetic acid with sodium hydroxide

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from direct light.
Do not shake.
If removed from the refrigerator, Prolia should be kept at controlled room temperature (up to 25°C) in the original carton and must be used within 30 days.

Nature and Contents of Container

Prolia is a sterile and preservative-free product.

Syringe

Single use pre-filled syringe with stainless steel 27 gauge needle.

Pack size of one, presented in blistered packaging (pre-filled syringe with a needle guard).

The pre-filled syringe is not made with natural rubber latex.

Instructions for Use/Handling

Before administration, the Prolia solution should be inspected for particulate matter and discolouration. The solution should not be used if cloudy or discoloured.

Do not shake.

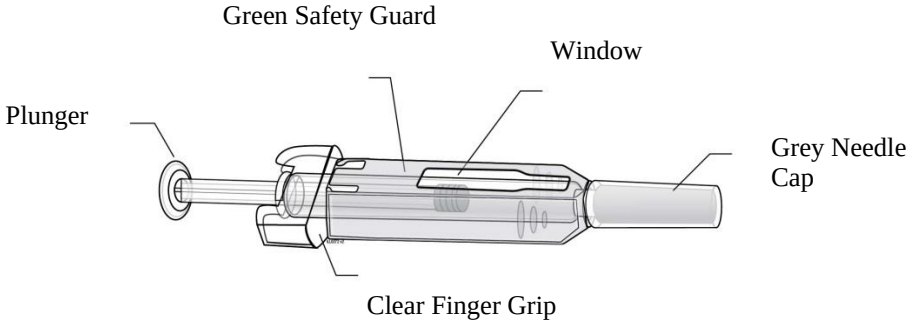
To avoid discomfort at the site of injection, allow the pre-filled syringe to reach room temperature (up to 25°C) before injecting and inject slowly. Inject the entire contents of the pre-filled syringe. Dispose of any medicinal product remaining in the pre-filled syringe.

Any unused product or waste material should be disposed of in accordance with local requirements.

INSTRUCTIONS FOR INJECTING WITH THE PROLIA PRE-FILLED SYRINGE WITH A MANUAL NEEDLE GUARD

IMPORTANT: In order to minimise accidental needlesticks, the Prolia single-use pre-filled syringe will have a green safety guard; manually activate the safety guard <u>after</u> the injection is given.

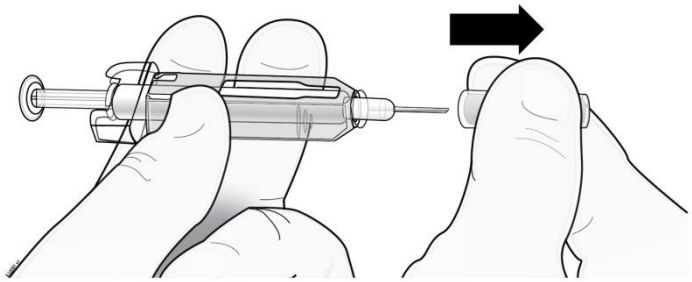
DO NOT slide the green safety guard forward over the needle before administering the injection; it will lock in place and prevent injection.



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

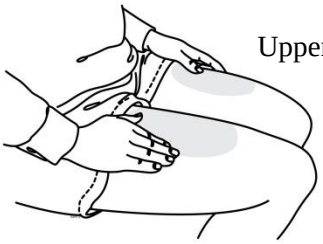
Step 1: Remove Grey Needle Cap

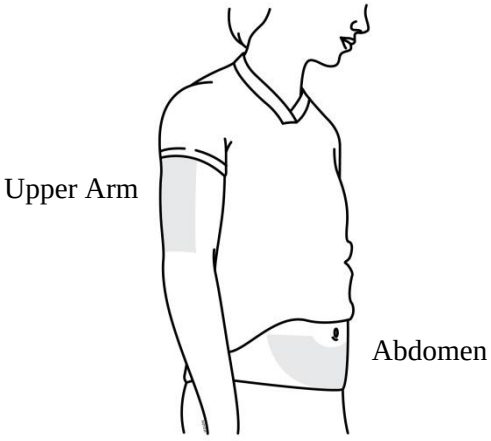
Remove needle cap.



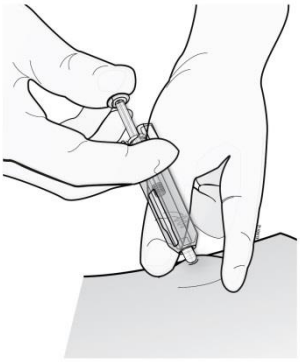
Step 2: Administer Subcutaneous Injection

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.



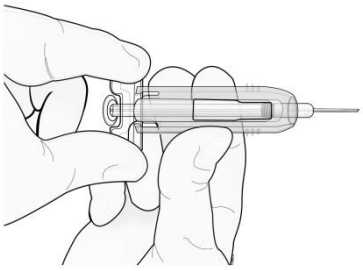
DO NOT put grey needle cap back on needle.

Step 3: Immediately Slide Green Safety Guard Over Needle

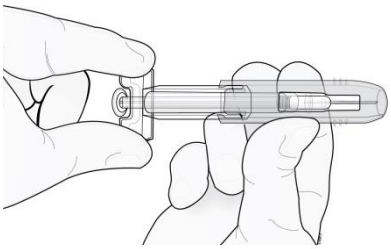
With the *needle pointing away from you…*

Hold the pre-filled syringe by the clear 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.

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Manufactured by: Amgen Manufacturing Limited, State Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777, USA

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