PROLIA ™
Denosumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each vial contains 60 mg denosumab 1.0 mL solution (60 mg/mL)

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

Postmenopausal Osteoporosis

PROLIA is indicated for the treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, *PROLIA* increases bone mineral density (BMD) and reduces the incidence of hip, vertebral and non-vertebral fractures.

Bone Loss in Patients Undergoing Hormone Ablation for Cancer

PROLIA is indicated for the treatment of bone loss in patients undergoing hormone ablation for prostate or breast cancer. In patients with prostate cancer, *PROLIA* reduces the incidence of vertebral fractures.

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 a single subcutanous injection of 60 mg administered once every 6 months.

Patients should receive calcium and vitamin D supplements whilst undergoing treatment.

Populations

Children

PROLIA is not recommended in paediatric patients as the safety and effectiveness of *PROLIA* have not been established in the paediatric age group. 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).

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

Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia (see Adverse Reactions).

Patients receiving *PROLIA* may develop skin infections (predominantly cellulitis) leading to hospitalisation. These events were reported more frequently in the denosumab (0.4%) versus the placebo (0.1%) groups. (see Adverse reactions). The overall incidence of skin infections was similar between the placebo and denosumab groups. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

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).

PROLIA contains the same active ingredient (denosumab) found in *XGEVA™*. Patients receiving *PROLIA* should not receive *XGEVA*.

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.

Interactions

PROLIA (60 mg subcutaneously) 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 (see Pharmacokinetics).

Pregnancy and Lactation

Pregnancy

There is no adequate data in pregnant women. *PROLIA* is not recommended for use in pregnant women.

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 (see Pre-clinical Safety Data).

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 maturation of the maternal mammary gland leading to impaired lactation post-partum.

Women who become pregnant during PROLIA treatment are encouraged to enrol in Amgen's Pregnancy Surveillance Program. Patients or their physicians should contact their local GSK representative to enrol.

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

Clinical Trial Data

Adverse reactions are listed below by MedDRA body system organ class and by frequency. The frequency categories based on one year event rates used are:

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100
Rare	≥ 1 in 10,000 and < 1 in 1,000
Very Rare	< 1/10,000

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]
Eye disorders	Common	Cataracts[2]
Skin and subcutaneous tissue disorders	Uncommon	Eczema[3]
Musculoskeletal and connective tissue disorders	Common Rare Very rare	Pain in extremity Osteonecrosis of the jaw Atypical femoral fracture[1,4]

[1] See Warnings and Precautions

[2] In men with prostate cancer receiving androgen deprivation therapy

[3] includes dermatitis, allergic dermatitis, atopic dermatitis and contact dermatitis.

[4] In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with *PROLIA*.

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 hypocalcemia receiving *PROLIA*.

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 1080 mg over 6 months).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of ActionDenosumab 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 makers) 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 metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the PK of drugs metabolized by 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 post-menopausal 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, non-vertbral and hip fractures in post-menopausal 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 non-vertebral 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 prespecified 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 non-vertebral 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 non-vertebral (16%) fractures.

Effect on all clinical fractures

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

Densoumab also reduced the risk of clinical (30% relative risk reduction, 2.9% unadjusted absolute risk reduction), major non-vertebral (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 non-vertebral fractures (35% relative risk reduction, 4.1% unadjusted absolute risk reduction, p < 0.001) over 3 years. Reductions in non-vertebral 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 4550 patients who completed the FREEDOM study (N = 7808) enrolled in a 7-year, multinational, multicenter, open label, single-arm extension study to evaluate the long-term safety and efficacy of Prolia. All patientsin the extension study received denosumab 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 from the first 2 years of the extension study for patients who received denosumab in the FREEDOM study and continued on therapy (years 4 and 5 of denosumab treatment), the overall subject incidence rates of adverse events and serious adverse events reported were similar to that observed in the initial 3 years of the FREEDOM study.

For patients who crossed over to denosumab from placebo in the FREEDOM study , the overall subject incidence rates of adverse events and serious adverse events reported also similar to the first 3 years of the FREEDOM study. Two cases of ONJ were observed; both resolved.

Denosumab treatment maintained a low incidence of new vertebral and non-vertebral fractures in years 4 and 5 (2.8% of patients had at least one new vertebral fracture by month 24, 2.5% of patients had a nonvertebral fracture).

Denosumab treatment continued to increase BMD at the lumbar spine (3.3%), total hip (1.3%), femoral neck (1.2%) and trochanter (1.8%) in years 4 and 5. Percent increase in BMD from the original FREEDOM study baseline (ie, after 5 years of treatment) in the long-term group was 13.8% at the lumbar spine, 7.0% at the total hip, 6.2% at the femoral neck and 9.7% at the trochanter.

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).

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

Treatment of bone loss associated with androgen deprivation

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). Denosumab also reduced the subject incidence of more than one osteoporotic fracture at any site by 72% relative to placebo over 3 years (placebo 2.5% vs. denosumab 0.7%, p = 0.0063).

Treatment of bone loss in women 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.

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 aromatase inhibitor therapy, weight/BMI, prior chemotherapy, prior selective estrogen receptor modulator (SERM) use, and time since menopause.

Pre-Clinical Safety Data

Carcinogenecity

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 ovariectomized 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 mineralization defects, accumulation of osteoid or woven bone.

Transition from 6-months treatment with alendronate to 25 mg/kg denosumab in ovariectomized 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 activity of denosumab.

In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal 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

Acetate
Sodium hydroxide
Sorbitol
Polysorbate 20 (Prefilled Syringe only)
Water for Injection

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 (store below 25°C or 30°C) in the original carton and must be used within 30 days.

The storage conditions depend on the locally registered shelf-life (refer to the pack for information).

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 (pre-filled syringe with or without a needle guard) or unblistered packaging (pre-filled syringe only).

The needle cover of the pre-filled syringe contains dry natural rubber, which is a derivative of latex. (see Instructions for Use/Handling).

Vial

One ml solution in a single use vial made from Type 1 glass.

Instructions for Use/Handling

Persons sensitive to latex should not handle the *[insert color if appropriate]* needle cap on the single use prefilled syringe, which contains dry natural rubber (a derivative of latex).

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

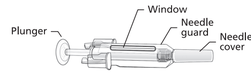
Instruction for self-administration by subcutaneous injection is included in the package leaflet.

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

Not all presentations are available in every country.

INSTRUCTIONS FOR INJECTING WITH THE PROLIA PRE-FILLED SYRINGE WITH AN AUTOMATIC NEEDLE GUARD

This section contains information on how to use the *PROLIA* pre-filled syringe. It is important that you or your carer do not give the injection unless training from your doctor or healthcare provider has been received. Always wash your hands before every injection. If you have questions about how to inject, please ask your doctor or healthcare provider for assistance.



Before you begin

Read all instructions thoroughly before using the pre-filled syringe.

To reduce the risk of accidental needle sticks to users, each pre-filled syringe comes with a needle guard that is automatically activated to cover the needle after complete delivery of the pre-filled syringe content.

DO NOT attempt to activate the needle guard prior to injection.

DO NOT use the pre-filled syringe if the needle cover has been removed, or the needle guard has been activated (covering the needle).

How do you use the *PROLIA* pre-filled syringe?

Your doctor has prescribed a *PROLIA* pre-filled syringe for injection into the tissue just under the skin (subcutaneous). You must inject the entire content (1 ml) of the *PROLIA* pre-filled syringe and it should be injected once every 6 months as instructed by your doctor or healthcare provider.

Equipment:

To give an injection, you will need:

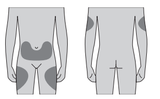
1. A new *PROLIA* pre-filled syringe; and
2. Alcohol wipes or similar.

What to do before you give a subcutaneous injection of *PROLIA*

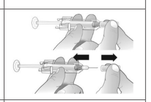
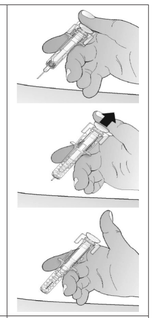
1. Remove the pre-filled syringe from the refrigerator.
   DO NOT pick up the pre-filled syringe by the plunger or needle cover. This could damage the device.
2. The pre-filled syringe may be left outside the refrigerator to reach room temperature. This will make the injection more comfortable.
   DO NOT warm it in any other way, for example, in a microwave or in hot water.
   DO NOT leave the syringe exposed to direct light..
3. **DO NOT** shake the pre-filled syringe excessively.
4. **DO NOT** remove the needle cover from the pre-filled syringe until you are ready to inject.
5. Check the expiry date on the pre-filled syringe label (EXP:).
   DO NOT use it if the date has passed the last day of the month shown.
6. Check the appearance of *PROLIA*.
   It must be a clear, colourless to slightly yellow solution.
   The solution should not be injected if it is cloudy or discoloured.
7. Find a comfortable, well-lit, clean surface and put all the equipment within reach.
8. Wash your hands thoroughly.

Where should you give the injection?

The best places to inject are the top of your thighs and the abdomen.
Your carer can also use the outer area of your upper arms.



How do you give the injection?

1. Disinfect the skin by using an alcohol wipe.	
2. To avoid bending the needle, gently pull the cover from the needle **straight off** without twisting, as shown. **DO NOT** touch the needle or push the plunger.	
3. You may notice a small bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.	
4. Pinch (without squeezing) the skin between your thumb and forefinger. Put the needle fully into the skin as shown by your doctor or healthcare provider.	
5. Push the plunger with a **slow** constant pressure, always keeping the skin pinched. Push the plunger all the way down as far as it will go to inject **all the solution**. The needle guard will not activate unless you empty the pre-filled syringe.	
6. While the plunger is still pressed all the way down, remove the needle and let go of the skin. Release the plunger and allow the syringe to move up until the entire needle is covered by the needle guard.	
7. If the needle guard is not activated, an incomplete injection may have occurred. Call your doctor or healthcare provider if you think you have not received the full dose. **DO NOT** put the needle cover back on used syringes.	
8. If you notice a spot of blood, you may gently dab it away with a cotton ball or tissue. Do not rub the injection site. If needed, you may cover the injection site with a plaster.	
9. Only use each pre-filled syringe for one injection. **DO NOT** use any *PROLIA* that is left in the syringe.	
Remember: If you have any problems, please ask your doctor or healthcare provider for help and advice.	

Disposing of used syringes

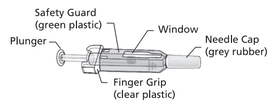
- **DO NOT** put the needle cover back on used syringes.
- Keep used syringes out of the reach and sight of children.

The used syringe should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

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

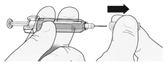


Activate the green safety guard (slide over the needle) after the injection.

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 Injection

Insert needle and inject all the liquid.

DO NOT put grey needle cap back on needle.

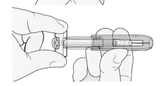
Step 3: Immediately Slide Green Safety Guard Over Needle

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.

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