ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prolia 60 mg solution for injection in a pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 60 mg of denosumab in 1 ml of solution (60 mg/ml).

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology.

Excipient with known effect:
Each ml of solution contains 47 mg sorbitol (E420) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.

Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.

4.2 Posology and method of administration

Posology
The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

Patients must be adequately supplemented with calcium and vitamin D (see section 4.4).

Patients with renal impairment
No dose adjustment is required in patients with renal impairment (see sections 4.4 and 5.2).

Patients with hepatic impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment (see section 5.2).

Elderly Patients (age ≥ 65)
No dose adjustment is required in elderly patients.

Paediatric population
Prolia is not recommended in paediatric patients (age < 18) as the safety and efficacy of Prolia in these patients have not been established. Inhibition of RANK/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption (see also section 5.3).

Method of administration
Administration should be performed by an individual who has been adequately trained in injection techniques. For subcutaneous use.

The instructions for use, handling and disposal are given in section 6.6.

4.3 Contraindications

- Hypocalcaemia (see section 4.4).

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Calcium and Vitamin D supplementation
Adequate intake of calcium and vitamin D is important in all patients.

Precautions for use

Hypocalcaemia
Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia.

In the post-marketing setting, severe symptomatic hypocalcaemia has been reported (see section 4.8).

Skin Infections
Patients receiving Prolia may develop skin infections (predominantly cellulitis) leading to hospitalisation (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Osteonecrosis of the Jaw (ONJ)
Osteonecrosis of the jaw (ONJ) has been reported in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis.

ONJ has been reported rarely in clinical studies in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis.

There have been reports of ONJ in clinical studies in patients with advanced cancer treated with denosumab at the studied dose of 120 mg administered monthly. Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, dental extractions, and co-morbid disorders (e.g., pre-existing dental disease, anaemia, coagulopathy, infection) and previous treatment with bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible.

Good oral hygiene practices should be maintained during treatment with Prolia. For patients who develop ONJ while on Prolia therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with Prolia, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation.

Atypical fractures of the femur
Atypical femoral fractures have been reported in patients receiving Prolia (see section 4.8). Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterize these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore the contralateral femur should be examined in Prolia-treated patients who have sustained a femoral shaft fracture. Discontinuation of Prolia therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit risk assessment. 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.

Dry natural rubber
The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Concomitant treatment with other denosumab-containing medicinal products
Patients being treated with Prolia should not be treated concomitantly with other denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours).

Warnings for Excipients
Patients with rare hereditary problems of fructose intolerance should not use Prolia.

This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In an interaction study, Prolia did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that Prolia should not alter the pharmacokinetics of drugs metabolized by CYP3A4.

There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is considered to be low.

In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy, based on data from a transition study (alendronate to denosumab).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Prolia in pregnant women. Reproductive toxicity was shown in a study of cynomolgus monkeys, dosed throughout pregnancy with denosumab at AUC exposures 119-fold higher than the human dose (see section 5.3).

Prolia is not recommended for use in pregnant women.

Women who become pregnant during Prolia treatment are encouraged to enrol in Amgen's Pregnancy Surveillance programme. Contact details are provided in section 6 of the Package Leaflet – Information for the user.

Breast-feeding
It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (the target of denosumab see section 5.1) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see section 5.3). A decision on whether to abstain from breast-feeding or to abstain from therapy with Prolia should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Prolia therapy to the woman.

Women who are nursing during Prolia treatment are encouraged to enrol in Amgen's Lactation Surveillance Program. Contact details are provided in section 6 of the Package Leaflet – Information for the user.

Fertility
No data are available on the effect of denosumab on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Prolia has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Prolia was similar in patients with osteoporosis and in breast or prostate cancer patients receiving hormone ablation in five Phase III placebo-controlled clinical trials.

Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures (see sections 4.4 and section 4.8 - description of selected adverse reactions) have been observed with Prolia.

Tabulated list of adverse reactions
The data in Table 1 below describe adverse reactions reported from Phase II and III clinical trials in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation; and/or spontaneous reporting.

The following convention has been used for the classification of the adverse reactions (see table 1): 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) based on crude incidence rates. Within each frequency grouping and system organ class, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation

MedDRA system organ class	Frequency category	Adverse reactions
Infections and infestations	Common	Urinary tract infection
	Common	Upper respiratory tract infection
	Uncommon	Diverticulitis[1]
	Uncommon	Cellulitis[1]
	Uncommon	Ear infection

MedDRA system organ class	Frequency category	Adverse reactions
Immune system disorders	Rare Rare	Drug hypersensitivity[1] Anaphylactic reaction[1]
Metabolism and nutrition disorders	Rare	Hypocalcaemia[1]
Nervous system disorders	Common	Sciatica
Eye disorders	Common	Cataracts[1]
Gastrointestinal disorders	Common Common	Constipation Abdominal discomfort
Skin and subcutaneous tissue disorders	Common Common	Rash Eczema
Musculoskeletal and connective tissue disorders	Very common Rare Rare	Pain in extremity Osteonecrosis of the jaw[1] Atypical femoral fractures[1]

[1] See section Description of selected adverse reactions

In a pooled analysis of data from all phase II and phase III placebo controlled studies, Influenza-like illness was reported with a crude incidence rate of 1.2% for denosumab and 0.7 % for placebo. Although this imbalance was identified via a pooled analysis, it was not identified via a stratified analysis.

Description of selected adverse reactions

Hypocalcaemia
In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/l) following Prolia administration. Declines of serum calcium levels (less than 1.88 mmol/l) were not reported in either the two phase III placebo-controlled clinical trials in patients receiving hormone ablation or the phase III placebo-controlled clinical trial in men with osteoporosis.

In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported in patients at increased risk of hypocalcaemia receiving Prolia.

Skin infections
In phase III placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the Prolia groups in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus Prolia [1.5%, 59 out of 4,050]); in men with osteoporosis (placebo [0.8%, 1 out of 120] versus Prolia [0%, 0 out of 120]) and in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus Prolia [1.4%, 12 out of 860]). Skin infections leading to hospitalisation were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving Prolia. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the Prolia (0.6%, 5 out of 860) groups in the breast and prostate cancer studies.

Osteonecrosis of the jaw
In clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation (12347 patients, 9912 treated ≥ 1 year), ONJ was reported rarely with Prolia (see section 4.4).

Atypical fractures of the femur
In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with Prolia (see section 4.4).

Cataracts
In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving androgen deprivation therapy (ADT) an imbalance in cataract adverse events was observed (4.7% denosumab, 1.2% placebo). No imbalance was observed in postmenopausal women or men with osteoporosis or in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer.

Diverticulitis
In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving ADT an imbalance in diverticulitis adverse events was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between treatment groups in postmenopausal women or men with osteoporosis and in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer.

Drug-related hypersensitivity reactions
In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving Prolia.

Other special populations
In clinical studies, patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose in clinical studies. 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 reactions were observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of bone diseases – Other drugs affecting bone structure and mineralization, ATC code: M05BX04

Mechanism of action
Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

Pharmacodynamic effects
Prolia treatment rapidly reduced the rate of bone turnover, reaching a nadir for the bone resorption marker serum type 1 C-telopeptides (CTX) (85% reduction) by 3 days, with reductions maintained over the 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 Prolia's effects on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Bone turnover markers generally reached pre-treatment levels

within 9 months after the last dose. Upon re-initiation, reductions in CTX by denosumab were similar to those observed in patients initiating primary denosumab treatment.

Immunogenicity
In clinical studies, neutralising antibodies have not been observed for Prolia. Using a sensitive immunoassay < 1% of patients treated with denosumab for up to 5 years tested positive for non neutralising binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.

Treatment of osteoporosis in postmenopausal women
Efficacy and safety of Prolia administered once every 6 months for 3 years were investigated in post-menopausal women (7,808 women aged 60-91 years, of which 23.6% had prevalent vertebral fractures) with baseline bone mineral density (BMD) T-scores at the lumbar spine or total hip between –2.5 and –4.0 and a mean absolute 10-year fracture probability of 18.60% (deciles: 7.9-32.4%) for major osteoporotic fracture and 7.22% (deciles: 1.4-14.9%) for hip fracture. Women with other diseases or on therapies that may affect bone were excluded from this study. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

Effect on vertebral fractures
Prolia significantly reduced the risk of new vertebral fractures at 1, 2 and 3 years ($p < 0.0001$) (see table 2).

Table 2 The effect of Prolia on the risk of new vertebral fractures

	Proportion of women with fracture (%)		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Placebo n = 3,906	Prolia n = 3,902		
0-1 year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)**
0-2 years	5.0	1.4	3.5 (2.7, 4.3)	71 (61,79)**
0-3 years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)*

*p < 0.0001, **p < 0.0001 – exploratory analysis

Effect on hip fractures
Prolia demonstrated a 40% relative reduction (0.5% absolute risk reduction) in the risk of hip fracture over 3 years ($p < 0.05$). The incidence of hip fracture was 1.2% in the placebo group compared to 0.7% in the Prolia group at 3 years.

In a post-hoc analysis in women > 75 years, a 62% relative risk reduction was observed with Prolia (1.4% absolute risk reduction, $p < 0.01$).

Effect on all clinical fractures
Prolia significantly reduced fractures across all fracture types/groups (see table 3).

Table 3 The effect of Prolia on the risk of clinical fractures over 3 years

	Proportion of women with fracture (%)[+]		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Placebo n = 3,906	Prolia n = 3,902		
Any clinical fracture[1]	10.2	7.2	2.9 (1.6, 4.2)	30 (19, 41)***
Clinical vertebral fracture	2.6	0.8	1.8 (1.2, 2.4)	69 (53, 80)***
Non-vertebral fracture[2]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)**
Major non-vertebral fracture[3]	6.4	5.2	1.2 (0.1, 2.2)	20 (3, 34)*
Major osteoporotic fracture[4]	8.0	5.3	2.7 (1.6, 3.9)	35 (22, 45)***

*p ≤ 0.05; **p = 0.0106 *(secondary endpoint included in multiplicity adjustment)*, ***p ≤ 0.0001

+ Event rates based on Kaplan-Meier estimates at 3 years.
(1) Includes clinical vertebral fractures and non-vertebral fractures.
(2) Excludes those of the vertebrae, skull, facial, mandible, metacarpus, and finger and toe phalanges.
(3) Includes pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip.
(4) Includes clinical vertebral, hip, forearm, and humerus fractures, as defined by the WHO.

In women with baseline femoral neck BMD ≤ -2.5, Prolia reduced the risk of non-vertebral fracture (35% relative risk reduction, 4.1% absolute risk reduction, $p < 0.001$, exploratory analysis).

The reduction in the incidence of new vertebral fractures, hip fractures and non-vertebral fractures by Prolia over 3 years were consistent regardless of the 10-year baseline fracture risk.

Effect on bone mineral density
Prolia significantly increased BMD at all clinical sites measured, versus placebo at 1, 2 and 3 years. Prolia 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 (all $p < 0.0001$).

In clinical studies examining the effects of discontinuation of Prolia, BMD returned to approximately pre-treatment levels and remained above placebo within 18 months of the last dose. These data indicate that continued treatment with Prolia is required to maintain the effect of the medicinal product. Re-initiation of Prolia resulted in gains in BMD similar to those when Prolia was first administered.

Open-label Extension Study in the Treatment of Postmenopausal Osteoporosis
A total of 4550 patients (2343 Prolia & 2207 placebo) who missed no more than one dose of investigational product in the pivotal study described above and completed all study visits agreed to enroll in a 7-year, multinational, multicenter, open label, single-arm extension study to evaluate the long-term safety and efficacy of Prolia. At month 24 of the extension study, after 5 years of denosumab treatment, the long-term group increased BMD by 13.8% at the lumbar spine, 7.0% at the total hip, 6.2% at the femoral neck and 9.7% at the trochanter from the original pivotal study baseline. Fracture incidence was evaluated as a safety endpoint: continued Prolia treatment maintained a low incidence of new vertebral and non-vertebral fractures in years 4 and 5 (annualised rate of new vertebral fracture was 1.4% in both years 4 and 5, while 1.4% and 1.1% of patients had a nonvertebral fracture in years 4 and 5 respectively). Three cases of osteonecrosis of the jaw (ONJ) occurred during the first 25 months in the study, two cases in the *de novo* treatment group and one case in the long term treatment group, all cases resolved.

Treatment of osteoporosis in men
Efficacy and safety of Prolia once every 6 months for 1 year were investigated in 242 men aged 31-84 years. Subjects with an eGFR < 30 ml/min/1.73 m^2 were excluded from the study. All men received calcium (at least 1,000 mg) and vitamin D (at least 800 IU) supplementation daily.

The primary efficacy variable was percent change in lumbar spine BMD, fracture efficacy was not evaluated. Prolia significantly increased BMD at all clinical sites measured, relative to placebo at 12 months: 4.8% at lumbar spine, 2.0% at total hip, 2.2% at femoral neck, 2.3% at hip trochanter, and 0.9% at distal 1/3 radius (all $p < 0.05$). Prolia increased lumbar spine BMD from baseline in 94.7% of men at 1 year. Significant increases in BMD at lumbar spine, total hip, femoral neck and hip trochanter were observed by 6 months ($p < 0.0001$).

Bone histology
Bone histology was evaluated in 62 postmenopausal women with osteoporosis or with low bone mass who were either naïve to osteoporosis therapies or had transitioned from previous alendronate therapy following 1-3 years treatment with Prolia. Bone histology was also evaluated in 17 men with osteoporosis following 1 year treatment with Prolia. Bone biopsy results from all studies showed bone

of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis.

Treatment of bone loss associated with androgen deprivation
Efficacy and safety of Prolia once every 6 months for 3 years were investigated in men with histologically confirmed non-metastatic prostate cancer receiving ADT (1,468 men aged 48-97 years) who were at increased risk of fracture (defined as > 70 years, or < 70 years with a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 or a history of an osteoporotic fracture.) All men received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

Prolia significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 3 years: 7.9% at the lumbar spine, 5.7% at the total hip, 4.9% at the femoral neck, 6.9% at the hip trochanter, 6.9% at the distal 1/3 radius and 4.7% at the total body (all $p < 0.0001$). In a prospectively planned exploratory analysis, significant increases in BMD were observed at the lumbar spine, total hip, femoral neck and the hip trochanter 1 month after the initial dose.

Prolia demonstrated a significant relative risk reduction of new vertebral fractures: 85% (1.6% absolute risk reduction) at 1 year, 69% (2.2% absolute risk reduction) at 2 years and 62% (2.4% absolute risk reduction) at 3 years (all $p < 0.01$).

Treatment of bone loss associated with adjuvant aromatase inhibitor therapy
Efficacy and safety of Prolia once every 6 months for 2 years was investigated in women with non-metastatic breast cancer (252 women aged 35-84 years) and baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip or femoral neck. All 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**.** Prolia significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 2 years: 7.6% at lumbar spine, 4.7% at total hip, 3.6% at femoral neck, 5.9% at hip trochanter, 6.1% at distal 1/3 radius and 4.2% at total body (all $p < 0.0001$).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Prolia in all subsets of the paediatric population in the treatment of bone loss associated with sex hormone ablative therapy, and in subsets of the paediatric population below the age of 2 in the treatment of osteoporosis. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Following subcutaneous administration of a 1.0 mg/kg dose, which approximates the approved 60 mg dose, exposure based on AUC was 78% as compared to intravenous administration at the same dose level. For a 60 mg subcutaneous dose, maximum serum denosumab concentrations (C_{max}) of 6 μg/ml (range 1-17 μg/ml) occurred in 10 days (range 2-28 days).

Biotransformation
Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination
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 (53%) of patients had no measurable amounts of denosumab detected at 6 months post-dose.

No accumulation or change in denosumab pharmacokinetics with time was observed upon subcutaneous multiple-dosing of 60 mg once every 6 months. Denosumab pharmacokinetics was not affected by the formation of binding antibodies to denosumab and was similar in men and women. Age (28-87 years), race and disease state (low bone mass or osteoporosis; prostate or breast cancer) do not appear to significantly affect the pharmacokinetics of denosumab.

A trend was observed between higher body weight and lower exposure based on AUC and C_{max}. However, the trend is not considered clinically important, since pharmacodynamic effects based on bone turnover markers and BMD increases were consistent across a wide range of body weight.

Linearity/non-linearity
In dose ranging studies, denosumab exhibited non-linear, dose-dependent pharmacokinetics, with lower clearance at higher doses or concentrations, but approximately dose-proportional increases in exposures for doses of 60 mg and greater.

Renal impairment
In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab.

Hepatic impairment
No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of denosumab is not expected to be affected by hepatic impairment.

Paediatric population
The pharmacokinetic profile in paediatric populations has not been assessed.

5.3 Preclinical safety data

In single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 100 to 150 times greater systemic exposure than the recommended human dose had no impact on cardiovascular physiology, male or female fertility, or produced specific target organ toxicity.

Standard tests to investigate the genotoxicity potential of denosumab have not been evaluated, since such tests are not relevant for this molecule. However, due to its character it is unlikely that denosumab has any potential for genotoxicity.

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

In preclinical studies conducted in knockout mice lacking RANK or RANKL, impairment of lymph node formation was observed in the foetus. An absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) was also observed in knockout mice lacking RANK or RANKL.

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. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain).

There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

In preclinical bone quality studies in monkeys on long-term denosumab treatment, decreases in bone turnover were associated with improvement in bone strength and normal bone histology. Calcium levels were transiently decreased and parathyroid hormone levels transiently increased in ovariectomised monkeys treated with denosumab.

In male mice genetically engineered to express huRANKL (knock-in mice), which were subjected to a transcortical fracture, denosumab delayed the removal of cartilage and remodelling of the fracture callus compared to control, but biomechanical strength was not adversely affected.

Knockout mice (see section 4.6) lacking RANK or RANKL exhibited decreased body weight, reduced bone growth and lack of tooth eruption. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with high doses of a construct of osteoprotegerin bound to Fc (OPG-Fc) was associated with inhibition of bone growth and tooth eruption. These changes were partially reversible in this model when dosing with RANKL inhibitors was discontinued. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid, glacial*
Sodium hydroxide (for pH adjustment)*
Sorbitol (E420)
Polysorbate 20
Water for injections
* Acetate buffer is formed by mixing acetic acid with sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Prolia may be stored at room temperature (up to 25°C) for up to 30 days in the original container. Once removed from the refrigerator, Prolia must be used within this 30 day period.

6.4 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 light.
Do not shake excessively.

6.5 Nature and contents of container

One ml solution in a single use pre-filled syringe made from type I glass with stainless steel 27 gauge needle, with or without needle guard.

The needle cover of the pre-filled syringe contains dry natural rubber, which is a derivative of latex (see section 4.4).

Pack size of one, presented in blistered (pre-filled syringe with or without a needle guard) or unblistered packaging (pre-filled syringe only).

6.6 Special precautions for disposal and other handling

Before administration, the Prolia solution should be inspected**.** Do not inject the solution if it contains particles, or is cloudy or discoloured. Do not shake excessively. 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/618/001
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 May 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Prolia 60 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 60 mg of denosumab in 1 ml of solution (60 mg/ml).

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology.

Excipient with known effect:
Each ml of solution contains 47 mg sorbitol (E420) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, colourless to slightly yellow solution and may contain trace amounts of translucent to white proteinaceous particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.

Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.

4.2 Posology and method of administration

Posology
The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

Patients must be adequately supplemented with calcium and vitamin D (see section 4.4).

Patients with renal impairment
No dose adjustment is required in patients with renal impairment (see sections 4.4 and 5.2).

Patients with hepatic impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment (see section 5.2).

Elderly Patients (age ≥ 65)
No dose adjustment is required in elderly patients.

Paediatric population
Prolia is not recommended in paediatric patients (age < 18) as the safety and efficacy of Prolia in these patients have not been established. Inhibition of RANK/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption (see also section 5.3).

Method of administration
Administration should be performed by an individual who has been adequately trained in injection techniques. For subcutaneous use.

The instructions for use, handling and disposal are given in section 6.6.

4.3 Contraindications

- Hypocalcaemia (see section 4.4).

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Calcium and Vitamin D supplementation
Adequate intake of calcium and vitamin D is important in all patients.

Precautions for use

Hypocalcaemia
Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia.

In the post-marketing setting, severe symptomatic hypocalcaemia has been reported (see section 4.8).

Skin Infections
Patients receiving Prolia may develop skin infections (predominantly cellulitis) leading to hospitalisation (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Osteonecrosis of the Jaw (ONJ)
Osteonecrosis of the jaw (ONJ) has been reported in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis.

ONJ has been reported rarely in clinical studies in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis.

There have been reports of ONJ in clinical studies in patients with advanced cancer treated with denosumab at the studied dose of 120 mg administered monthly. Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, dental extractions, and co-morbid disorders (e.g., pre-existing dental disease, anaemia, coagulopathy, infection) and previous treatment with bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible.

Good oral hygiene practices should be maintained during treatment with Prolia. For patients who develop ONJ while on Prolia therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with Prolia, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation.

Atypical fractures of the femur
Atypical femoral fractures have been reported in patients receiving Prolia (see section 4.8). Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterize these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore the contralateral femur should be examined in Prolia-treated patients who have sustained a femoral shaft fracture. Discontinuation of Prolia therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit risk assessment. 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.

Concomitant treatment with other denosumab-containing medicinal products
Patients being treated with Prolia should not be treated concomitantly with other denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours).

Warnings for Excipients
Patients with rare hereditary problems of fructose intolerance should not use Prolia.

This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In an interaction study, Prolia did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that Prolia should not alter the pharmacokinetics of drugs metabolized by CYP3A4.

There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is considered to be low.

In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy, based on data from a transition study (alendronate to denosumab).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Prolia in pregnant women. Reproductive toxicity was shown in a study of cynomolgus monkeys, dosed throughout pregnancy with denosumab at AUC exposures 119-fold higher than the human dose (see section 5.3).

Prolia is not recommended for use in pregnant women.

Women who become pregnant during Prolia treatment are encouraged to enrol in Amgen’s Pregnancy Surveillance programme. Contact details are provided in section 6 of the Package Leaflet – Information for the user.

Breast-feeding
It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (the target of denosumab see section 5.1) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see section 5.3). A decision on whether to abstain from breast-feeding or to abstain from therapy with Prolia should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Prolia therapy to the woman.

Women who are nursing during Prolia treatment are encouraged to enrol in Amgen's Lactation Surveillance Program. Contact details are provided in section 6 of the Package Leaflet – Information for the user.

Fertility
No data are available on the effect of denosumab on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Prolia has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Prolia was similar in patients with osteoporosis and in breast or prostate cancer patients receiving hormone ablation in five Phase III placebo-controlled clinical trials.

Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures (see sections 4.4 and section 4.8 - description of selected adverse reactions) have been observed with Prolia.

Tabulated list of adverse reactions
The data in Table 1 below describe adverse reactions reported from Phase II and III clinical trials in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation; and/or spontaneous reporting.

The following convention has been used for the classification of the adverse reactions (see table 1): 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) based on crude incidence rates. Within each frequency grouping and system organ class, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation

MedDRA system organ class	Frequency category	Adverse reactions
Infections and infestations	Common	Urinary tract infection
	Common	Upper respiratory tract infection
	Uncommon	Diverticulitis[1]
	Uncommon	Cellulitis[1]
	Uncommon	Ear infection
Immune system disorders	Rare	Drug hypersensitivity[1]
	Rare	Anaphylactic reaction[1]
Metabolism and nutrition disorders	Rare	Hypocalcaemia[1]

MedDRA system organ class	Frequency category	Adverse reactions
Nervous system disorders	Common	Sciatica
Eye disorders	Common	Cataracts[1]
Gastrointestinal disorders	Common Common	Constipation Abdominal discomfort
Skin and subcutaneous tissue disorders	Common Common	Rash Eczema
Musculoskeletal and connective tissue disorders	Very common Rare Rare	Pain in extremity Osteonecrosis of the jaw[1] Atypical femoral fractures[1]

[1] See section Description of selected adverse reactions

In a pooled analysis of data from all phase II and phase III placebo controlled studies, Influenza-like illness was reported with a crude incidence rate of 1.2% for denosumab and 0.7 % for placebo. Although this imbalance was identified via a pooled analysis, it was not identified via a stratified analysis.

Description of selected adverse reactions

Hypocalcaemia
In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/l) following Prolia administration. Declines of serum calcium levels (less than 1.88 mmol/l) were not reported in either the two phase III placebo-controlled clinical trials in patients receiving hormone ablation or the phase III placebo-controlled clinical trial in men with osteoporosis.

In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported in patients at increased risk of hypocalcaemia receiving Prolia.

Skin infections
In phase III placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the Prolia groups in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus Prolia [1.5%, 59 out of 4,050]), in men with osteoporosis (placebo [0.8%, 1 out of 120] versus Prolia [0%, 0 out of 120]) and in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus Prolia [1.4%, 12 out of 860]). Skin infections leading to hospitalisation were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving Prolia. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the Prolia (0.6%, 5 out of 860) groups in the breast and prostate cancer studies.

Osteonecrosis of the jaw
In clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation (12347 patients, 9912 treated ≥ 1 year), ONJ was reported rarely with Prolia (see section 4.4).

Atypical fractures of the femur
In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with Prolia (see section 4.4).

Cataracts
In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving androgen deprivation therapy (ADT) an imbalance in cataract adverse events was observed (4.7% denosumab, 1.2% placebo). No imbalance was observed in postmenopausal women or men with osteoporosis or in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer.

Diverticulitis
In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving ADT an imbalance in diverticulitis adverse events was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between treatment groups in postmenopausal women or men with osteoporosis and in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer.

Drug-related hypersensitivity reactions
In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving Prolia.

Other special populations
In clinical studies, patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose in clinical studies. 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 reactions were observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of bone diseases – Other drugs affecting bone structure and mineralization, ATC code: M05BX04

Mechanism of action
Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

Pharmacodynamic effects
Prolia treatment rapidly reduced the rate of bone turnover, reaching a nadir for the bone resorption marker serum type 1 C-telopeptides (CTX) (85% reduction) by 3 days, with reductions maintained over the 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 Prolia's effects on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Bone turnover markers generally reached pre-treatment levels within 9 months after the last dose. Upon re-initiation, reductions in CTX by denosumab were similar to those observed in patients initiating primary denosumab treatment.

Immunogenicity
In clinical studies, neutralising antibodies have not been observed for Prolia. Using a sensitive immunoassay < 1% of patients treated with denosumab for up to 5 years tested positive for non

neutralising binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.

Treatment of osteoporosis in postmenopausal women

Efficacy and safety of Prolia administered once every 6 months for 3 years were investigated in post-menopausal women (7,808 women aged 60-91 years, of which 23.6% had prevalent vertebral fractures) with baseline bone mineral density (BMD) T-scores at the lumbar spine or total hip between –2.5 and –4.0 and a mean absolute 10-year fracture probability of 18.60% (deciles: 7.9-32.4%) for major osteoporotic fracture and 7.22% (deciles: 1.4-14.9%) for hip fracture. Women with other diseases or on therapies that may affect bone were excluded from this study. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

Effect on vertebral fractures

Prolia significantly reduced the risk of new vertebral fractures at 1, 2 and 3 years ($p < 0.0001$) (see table 2).

Table 2 The effect of Prolia on the risk of new vertebral fractures

	Proportion of women with fracture (%)		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Placebo n = 3,906	Prolia n = 3,902		
0-1 year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)**
0-2 years	5.0	1.4	3.5 (2.7, 4.3)	71 (61,79)**
0-3 years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)*

*$p < 0.0001$, **$p < 0.0001$ – exploratory analysis

Effect on hip fractures

Prolia demonstrated a 40% relative reduction (0.5% absolute risk reduction) in the risk of hip fracture over 3 years ($p < 0.05$). The incidence of hip fracture was 1.2% in the placebo group compared to 0.7% in the Prolia group at 3 years.

In a post-hoc analysis in women > 75 years, a 62% relative risk reduction was observed with Prolia (1.4% absolute risk reduction, $p < 0.01$).

Effect on all clinical fractures

Prolia significantly reduced fractures across all fracture types/groups (see table 3).

Table 3 The effect of Prolia on the risk of clinical fractures over 3 years

	Proportion of women with fracture (%)+		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Placebo n = 3,906	Prolia n = 3,902		
Any clinical fracture[1]	10.2	7.2	2.9 (1.6, 4.2)	30 (19, 41)***
Clinical vertebral fracture	2.6	0.8	1.8 (1.2, 2.4)	69 (53, 80)***
Non-vertebral fracture[2]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)**
Major non-vertebral fracture[3]	6.4	5.2	1.2 (0.1, 2.2)	20 (3, 34)*
Major osteoporotic fracture[4]	8.0	5.3	2.7 (1.6, 3.9)	35 (22, 45)***

*$p \leq 0.05$; **$p = 0.0106$ *(secondary endpoint included in multiplicity adjustment)*, ***$p \leq 0.0001$

+ Event rates based on Kaplan-Meier estimates at 3 years.

(1) Includes clinical vertebral fractures and non-vertebral fractures.

(2) Excludes those of the vertebrae, skull, facial, mandible, metacarpus, and finger and toe phalanges.

(3) Includes pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip.

(4) Includes clinical vertebral, hip, forearm, and humerus fractures, as defined by the WHO.

In women with baseline femoral neck BMD ≤ -2.5, Prolia reduced the risk of non-vertebral fracture (35% relative risk reduction, 4.1% absolute risk reduction, $p < 0.001$, exploratory analysis).

The reduction in the incidence of new vertebral fractures, hip fractures and non-vertebral fractures by Prolia over 3 years were consistent regardless of the 10-year baseline fracture risk.

Effect on bone mineral density
Prolia significantly increased BMD at all clinical sites measured, versus placebo at 1, 2 and 3 years. Prolia 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 (all $p < 0.0001$).

In clinical studies examining the effects of discontinuation of Prolia, BMD returned to approximately pre-treatment levels and remained above placebo within 18 months of the last dose. These data indicate that continued treatment with Prolia is required to maintain the effect of the medicinal product. Re-initiation of Prolia resulted in gains in BMD similar to those when Prolia was first administered.

Open-label Extension Study in the Treatment of Postmenopausal Osteoporosis
A total of 4550 patients (2343 Prolia & 2207 placebo) who missed no more than one dose of investigational product in the pivotal study described above and completed all study visits agreed to enroll in a 7-year, multinational, multicenter, open label, single-arm extension study to evaluate the long-term safety and efficacy of Prolia. At month 24 of the extension study, after 5 years of denosumab treatment, the long-term group increased BMD by 13.8% at the lumbar spine, 7.0% at the total hip, 6.2% at the femoral neck and 9.7% at the trochanter from the original pivotal study baseline. Fracture incidence was evaluated as a safety endpoint: continued Prolia treatment maintained a low incidence of new vertebral and non-vertebral fractures in years 4 and 5 (annualised rate of new vertebral fracture was 1.4% in both years 4 and 5, while 1.4% and 1.1% of patients had a nonvertebral fracture in years 4 and 5 respectively). Three cases of osteonecrosis of the jaw (ONJ) occurred during the first 25 months in the study, two cases in the *de novo* treatment group and one case in the long term treatment group, all cases resolved.

Treatment of osteoporosis in men
Efficacy and safety of Prolia once every 6 months for 1 year were investigated in 242 men aged 31-84 years. Subjects with an eGFR < 30 ml/min/1.73 m^2 were excluded from the study. All men received calcium (at least 1,000 mg) and vitamin D (at least 800 IU) supplementation daily.

The primary efficacy variable was percent change in lumbar spine BMD, fracture efficacy was not evaluated. Prolia significantly increased BMD at all clinical sites measured, relative to placebo at 12 months: 4.8% at lumbar spine, 2.0% at total hip, 2.2% at femoral neck, 2.3% at hip trochanter, and 0.9% at distal 1/3 radius (all $p < 0.05$). Prolia increased lumbar spine BMD from baseline in 94.7% of men at 1 year. Significant increases in BMD at lumbar spine, total hip, femoral neck and hip trochanter were observed by 6 months ($p < 0.0001$).

Bone histology
Bone histology was evaluated in 62 postmenopausal women with osteoporosis or with low bone mass who were either naïve to osteoporosis therapies or had transitioned from previous alendronate therapy following 1-3 years treatment with Prolia. Bone histology was also evaluated in 17 men with osteoporosis following 1 year treatment with Prolia. Bone biopsy results from all studies showed bone of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis.

Treatment of bone loss associated with androgen deprivation
Efficacy and safety of Prolia once every 6 months for 3 years were investigated in men with histologically confirmed non-metastatic prostate cancer receiving ADT (1,468 men aged 48-97 years) who were at increased risk of fracture (defined as > 70 years, or < 70 years with a BMD T-score at the

lumbar spine, total hip, or femoral neck < -1.0 or a history of an osteoporotic fracture.) All men received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

Prolia significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 3 years: 7.9% at the lumbar spine, 5.7% at the total hip, 4.9% at the femoral neck, 6.9% at the hip trochanter, 6.9% at the distal 1/3 radius and 4.7% at the total body (all $p < 0.0001$). In a prospectively planned exploratory analysis, significant increases in BMD were observed at the lumbar spine, total hip, femoral neck and the hip trochanter 1 month after the initial dose.

Prolia demonstrated a significant relative risk reduction of new vertebral fractures: 85% (1.6% absolute risk reduction) at 1 year, 69% (2.2% absolute risk reduction) at 2 years and 62% (2.4% absolute risk reduction) at 3 years (all $p < 0.01$).

Treatment of bone loss associated with adjuvant aromatase inhibitor therapy
Efficacy and safety of Prolia once every 6 months for 2 years was investigated in women with non-metastatic breast cancer (252 women aged 35-84 years) and baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip or femoral neck. All 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**.** Prolia significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 2 years: 7.6% at lumbar spine, 4.7% at total hip, 3.6% at femoral neck, 5.9% at hip trochanter, 6.1% at distal 1/3 radius and 4.2% at total body (all $p < 0.0001$).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Prolia in all subsets of the paediatric population in the treatment of bone loss associated with sex hormone ablative therapy, and in subsets of the paediatric population below the age of 2 in the treatment of osteoporosis. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Following subcutaneous administration of a 1.0 mg/kg dose, which approximates the approved 60 mg dose, exposure based on AUC was 78% as compared to intravenous administration at the same dose level. For a 60 mg subcutaneous dose, maximum serum denosumab concentrations (C_{max}) of 6 μg/ml (range 1-17 μg/ml) occurred in 10 days (range 2-28 days).

Biotransformation
Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids

Elimination
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 (53%) of patients had no measurable amounts of denosumab detected at 6 months post-dose.

No accumulation or change in denosumab pharmacokinetics with time was observed upon subcutaneous multiple-dosing of 60 mg once every 6 months. Denosumab pharmacokinetics was not affected by the formation of binding antibodies to denosumab and was similar in men and women. Age (28-87 years)**,** race and disease state (low bone mass or osteoporosis; prostate or breast cancer) do not appear to significantly affect the pharmacokinetics of denosumab.

A trend was observed between higher body weight and lower exposure based on AUC and C_{max}. However, the trend is not considered clinically important, since pharmacodynamic effects based on bone turnover markers and BMD increases were consistent across a wide range of body weight.

Linearity/non-linearity
In dose ranging studies, denosumab exhibited non-linear, dose-dependent pharmacokinetics, with lower clearance at higher doses or concentrations, but approximately dose-proportional increases in exposures for doses of 60 mg and greater.

Renal impairment
In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab.

Hepatic impairment
No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of denosumab is not expected to be affected by hepatic impairment.

Paediatric population
The pharmacokinetic profile in paediatric populations has not been assessed.

5.3 Preclinical safety data

In single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 100 to 150 times greater systemic exposure than the recommended human dose had no impact on cardiovascular physiology, male or female fertility, or produced specific target organ toxicity.

Standard tests to investigate the genotoxicity potential of denosumab have not been evaluated, since such tests are not relevant for this molecule. However, due to its character it is unlikely that denosumab has any potential for genotoxicity.

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

In preclinical studies conducted in knockout mice lacking RANK or RANKL, impairment of lymph node formation was observed in the foetus. An absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) was also observed in knockout mice lacking RANK or RANKL.

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. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

In preclinical bone quality studies in monkeys on long-term denosumab treatment, decreases in bone turnover were associated with improvement in bone strength and normal bone histology. Calcium

levels were transiently decreased and parathyroid hormone levels transiently increased in ovariectomised monkeys treated with denosumab.

In male mice genetically engineered to express huRANKL (knock-in mice), which were subjected to a transcortical fracture, denosumab delayed the removal of cartilage and remodelling of the fracture callus compared to control, but biomechanical strength was not adversely affected.

Knockout mice (see section 4.6) lacking RANK or RANKL exhibited decreased body weight, reduced bone growth and lack of tooth eruption. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with high doses of a construct of osteoprotegerin bound to Fc (OPG-Fc) was associated with inhibition of bone growth and tooth eruption. These changes were partially reversible in this model when dosing with RANKL inhibitors was discontinued. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid, glacial*
Sodium hydroxide (for pH adjustment)*
Sorbitol (E420)
Water for injections
* Acetate buffer is formed by mixing acetic acid with sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Prolia may be stored at room temperature (up to 25°C) for up to 30 days in the original container. Once removed from the refrigerator, Prolia must be used within this 30 day period.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Do not shake excessively.

6.5 Nature and contents of container

One ml solution in a single use vial (type I glass) with stopper (fluoropolymer coated elastomeric) and seal (aluminium) with flip-off cap.

Pack size of one.

6.6 Special precautions for disposal and other handling

Before administration, the Prolia solution should be inspected. The solution may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discoloured. Do not shake excessively. To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting and inject slowly. Inject the entire contents of the vial. Dispose of any medicinal product remaining in the vial.

A 27 gauge needle is recommended for the administration of denosumab. Do not re-enter the vial.

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

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/618/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 May 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
D-88397 Biberach an der Riss
Germany

Amgen Inc.
4000 Nelson Road, Longmont, CO 80503
United States

Amgen Inc.
5550 Airport Boulevard, Boulder, CO 80301
United States

Amgen Inc.
One Amgen Center Drive,
Thousand Oaks, CA 91320
United States

Amgen Manufacturing Limited
PO Box 4060, Road 31 km 24.6,
Juncos, PR 00777-4060
Puerto Rico

Name and address of the manufacturers responsible for batch release

Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

Amgen Technology Ireland (ADL)
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Prolia 60 mg solution for injection in a pre-filled syringe
denosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml pre-filled syringe containing 60 mg of denosumab (60 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, glacial, sodium hydroxide, sorbitol (E420), polysorbate 20 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
One pre-filled syringe with automatic needle guard.
One pre-filled syringe.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Important: read the package leaflet before handling pre-filled syringe.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake excessively.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
NL-4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/618/001
EU/1/10/618/002
EU/1/10/618/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prolia

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERED PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Prolia 60 mg injection
denosumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

SC

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL (UNBLISTERED)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prolia 60 mg injection
denosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL (BLISTERED)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prolia 60 mg
denosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Prolia 60 mg solution for injection
denosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 60 mg of denosumab in 1 ml of solution (60 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, glacial, sodium hydroxide, sorbitol (E420) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
One vial.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake excessively.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
NL-4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/618/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prolia

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prolia 60 mg injection
denosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

REMINDER STICKERS TEXT (included in pack)

Next injection

Prolia 60 mg injection
denosumab

SC

Every 6 months

Amgen Europe B.V.

<…./…./….>

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Prolia 60 mg solution for injection in a pre-filled syringe
denosumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Prolia is and what it is used for

What Prolia is and how it works

Prolia contains denosumab, a protein (monoclonal antibody) that interferes with the action of another protein, in order to treat bone loss and osteoporosis. Treatment with Prolia makes bone stronger and less likely to break.

Bone is a living tissue and is renewed all the time. Oestrogen helps keep bones healthy. After the menopause, oestrogen level drops which may cause bones to become thin and fragile. This can eventually lead to a condition called osteoporosis. Osteoporosis can also occur in men due to a number of causes including ageing and/or a low level of the male hormone, testosterone. Many patients with osteoporosis have no symptoms, but they are still at risk of breaking bones, especially in the spine, hips and wrists.

Surgery or medicines that stop the production of oestrogen or testosterone used to treat patients with breast or prostate cancer can also lead to bone loss. The bones become weaker and break more easily.

What Prolia is used for

Prolia is used to treat:
- osteoporosis in women after the menopause (postmenopausal), reducing the risk of spinal, non-spinal and hip fractures; and osteoporosis in men.
- bone loss that results from a reduction in hormone (testosterone) level caused by surgery or treatment with medicines in patients with prostate cancer.

2. What you need to know before you use Prolia

Do not use Prolia

- if you have low calcium levels in the blood (hypocalcaemia).

- if you are allergic to denosumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before using Prolia

Please tell your doctor immediately if you develop a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), and possibly with symptoms of fever while being on treatment with Prolia.

Please tell your doctor if you have an allergy to latex (the needle cover on the pre-filled syringe contains a derivative of latex).

Tell your doctor if you have or have ever had severe kidney problems, kidney failure or have needed dialysis, which may increase your risk of getting low blood calcium if you do not take calcium supplements.

You should also take calcium and vitamin D supplements while being on treatment with Prolia. Your doctor will discuss this with you.

A dental examination should be considered before you start treatment with Prolia if you have cancer, are undergoing chemotherapy or radiotherapy, are taking steroids, do not receive routine dental care or have gum disease.

If you are under dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Prolia.

It is important to maintain good oral hygiene when being on treatment with Prolia.

Children and adolescents

Prolia is not recommended for children and adolescents under 18 years of age. The use of Prolia in children and adolescents has not been studied.

Other medicines and Prolia

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is especially important that you tell your doctor if you are being treated with another medicine containing denosumab.

You should not take Prolia together with another medicine containing denosumab .

Pregnancy and breast-feeding

Prolia has not been tested in pregnant women. It is important to tell your doctor if you are pregnant; think you may be pregnant; or plan to get pregnant. Prolia is not recommended for use if you are pregnant.

If you become pregnant during Prolia treatment, please inform your doctor. You may be encouraged to enrol in Amgen’s Pregnancy Surveillance programme. Local representative contact details are provided in section 6 of this leaflet.

It is not known whether Prolia is excreted in breast milk. It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding,

or whether to stop taking Prolia, considering the benefit of breast-feeding to the baby and the benefit of Prolia to the mother.

If you are nursing during Prolia treatment, please inform your doctor. You may be encouraged to enrol in Amgen's Lactation Surveillance Program. Local representative contact details are provided in section 6 of this leaflet.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Prolia has no or negligible influence on the ability to drive and use machines.

Prolia contains sorbitol (E420)

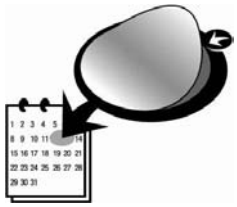
If you have been told by your doctor that you have an intolerance to some sugars (sorbitol E420), contact your doctor before taking this medicinal product.

If you are on a controlled sodium diet

This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg, i.e. essentially 'sodium-free'.

3. How to use Prolia

The recommended dose is one pre-filled syringe of 60 mg administered once every 6 months, as a single injection under the skin (subcutaneous). 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 arm. Each pack of Prolia contains a reminder card with stickers that can be removed from the carton. Use the peel-off stickers to mark the next injection date on your personal calendar and/or the reminder card to keep a record of the next injection date.



You should also take calcium and vitamin D supplements while being on treatment with Prolia. Your doctor will discuss this with you.

Your doctor may decide that it is best for you or a carer to inject Prolia. Your doctor or healthcare provider will show you or your carer how to use Prolia. For instructions on how to inject Prolia, please read the section at the end of this leaflet.

If you forget to use Prolia

If a dose of Prolia is missed, the injection should be administered as soon as possible. Thereafter, injections should be scheduled every 6 months from the date of the last injection.

If you stop using Prolia

To get the most benefit from your treatment, it is important to use Prolia for as long as your doctor prescribes it for you. Please talk to your doctor before you consider stopping the treatment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Uncommonly, patients receiving Prolia may develop skin infections (predominantly cellulitis). **Please tell your doctor immediately** if you develop any of these symptoms while being on treatment with Prolia: swollen, red area of skin, most commonly in the lower leg, that feels hot and tender, and possibly with symptoms of fever.

Very common side effects (affects more than 1 in 10 people)**:**

- arm or leg pain (pain in extremity).

Common side effects (affects 1 to 10 users in 100):

- painful urination, frequent urination, blood in the urine, inability to hold your urine,
- upper respiratory tract infection,
- pain, tingling or numbness that moves down your leg (sciatica),
- cloudy area in the lens of the eye (cataracts),
- constipation,
- abdominal discomfort,
- rash,
- skin condition with itching, redness and/or dryness (eczema).

Uncommon side effects (affects 1 to 10 users in 1,000):

- fever, vomiting and abdominal pain or discomfort (diverticulitis),
- ear infection.

Rare side effects (affects 1 to 10 users in 10,000):

- persistent pain and/or non-healing sores of the mouth or jaw,
- spasms, twitches, or cramps in your muscles, and/or numbness or tingling in your fingers, toes or around your mouth. These could be signs that you have low calcium levels in the blood (hypocalcaemia),
- allergic reactions (e.g. swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin, wheezing or difficulty breathing).

Unusual fractures of the thigh bone may occur rarely. Contact your doctor if you experience new or unusual pain in your hip, groin or thigh while being on treatment with Prolia as this may be an early indication of a possible fracture of the thigh bone.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Prolia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Store in the original carton in order to protect from light.
Do not shake excessively.

Your pre-filled syringe may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. Once your syringe has been left to reach room temperature (up to 25°C), it must be used within 30 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Prolia contains

- The active substance is denosumab. Each 1 ml pre-filled syringe contains 60 mg of denosumab (60 mg/ml).
- The other ingredients are acetic acid, glacial, sodium hydroxide, sorbitol (E420), polysorbate 20 and water for injections.

What Prolia looks like and contents of the pack

Prolia is a clear, colourless to slightly yellow solution for injection provided in a ready to use pre-filled syringe.

Each pack contains one pre-filled syringe with a needle guard.
Each pack contains one pre-filled syringe.

Marketing Authorisation Holder and Manufacturer
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder:
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Manufacturer:
Amgen Technology Ireland (ADL)
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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România
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Slovenija
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Slovenská republika
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Sverige
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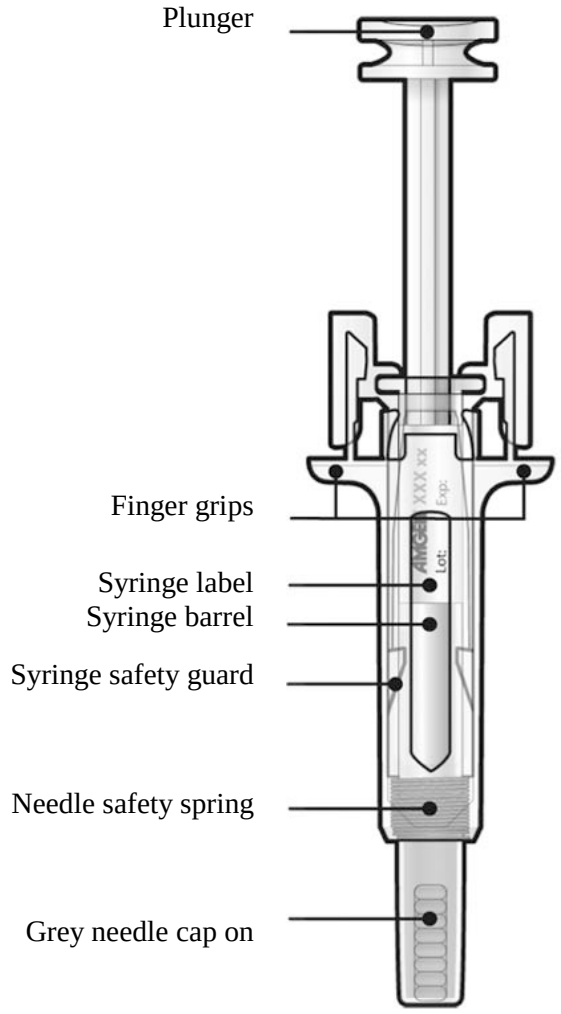
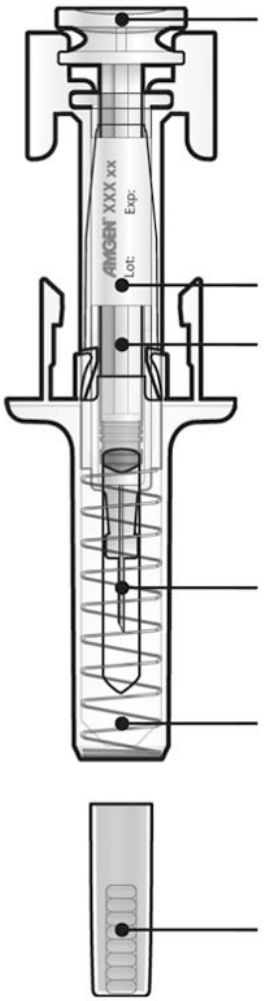
This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

Instructions for use:

Guide to parts	
Before use	After use
	

Important
Before you use a Prolia pre-filled syringe with automatic needle guard, read this important information: ✘ It is important that you do not try to give yourself the injection unless you have received training from your doctor or healthcare provider. ✘ Prolia is given as an injection into the tissue just under the skin (subcutaneous injection). ✘ Tell your doctor if you have an allergy to latex (the needle cover on the pre-filled syringe contains a derivative of latex). ✘ **Do not** remove grey needle cap from the pre-filled syringe until you are ready to inject. ✘ **Do not** use the pre-filled syringe if it has been dropped on a hard surface. Use a new pre-filled syringe and call your doctor or healthcare provider. ✘ **Do not** attempt to activate the pre-filled syringe prior to injection. ✘ **Do not** attempt to remove the clear pre-filled syringe safety guard from the pre-filled syringe. Call your doctor or healthcare provider if you have any questions.

Step 1: Prepare	
A	Remove the pre-filled syringe tray from the package and gather supplies needed for your injection.

For a more comfortable injection, leave the pre-filled syringe at room temperature for about 30 minutes before injecting. Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the new pre-filled syringe. Locate alcohol wipes, cotton ball or gauze pad, plaster and sharps disposal container (not included).

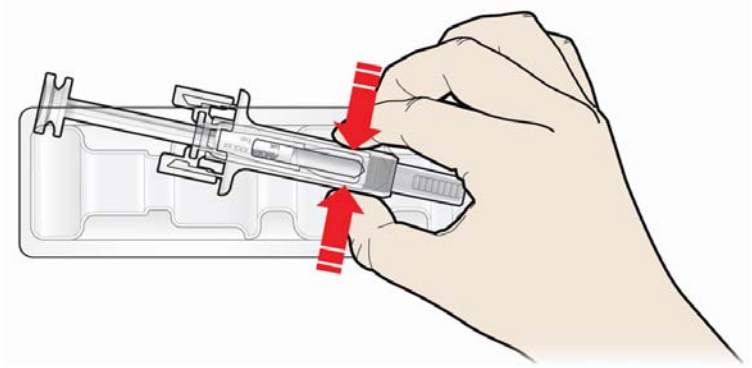
✘ **Do not** try to warm syringe by using a heat source such as hot water or microwave

✘ **Do not** leave the pre-filled syringe exposed to direct sunlight

✘ **Do not** shake the pre-filled syringe

✘ **Keep pre-filled syringes out of the sight and reach of children**

B	Open tray, peeling away cover. Grab pre-filled syringe safety guard to remove pre-filled syringe from tray.



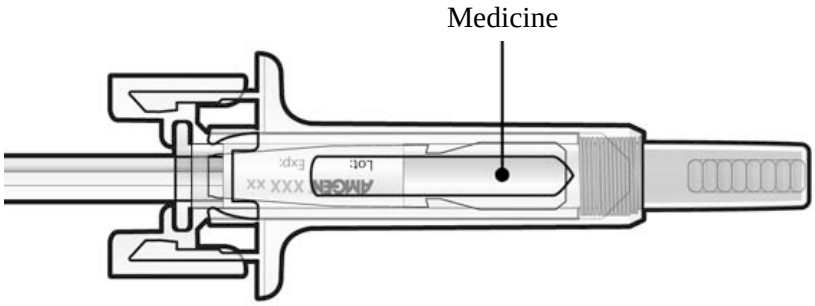
Grab here

For safety reasons:

✘ **Do not** grasp the plunger

✘ **Do not** grasp the grey needle cap

C	Inspect medicine and pre-filled syringe.

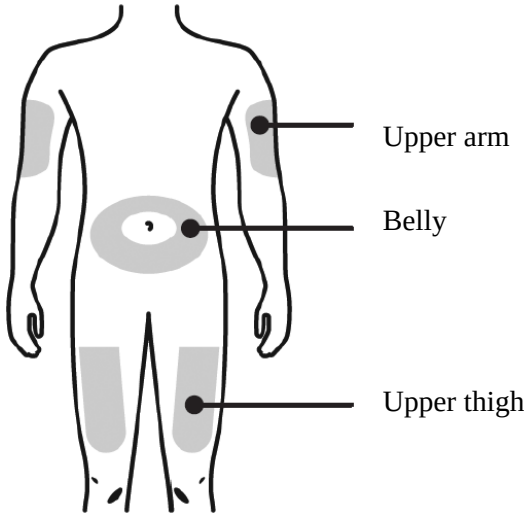


✘ **Do not** use the pre-filled syringe if:

- The medicine is cloudy or there are particles in it. It must be a clear, colourless to slightly yellow solution.
- Any part appears cracked or broken.
- The grey needle cap is missing or not securely attached.
- The expiry date printed on the label has passed the last day of the month shown.

In all cases, call your doctor or healthcare provider.

Step 2: Get ready	
A	Wash hands thoroughly. Prepare and clean your injection site.



You can use:

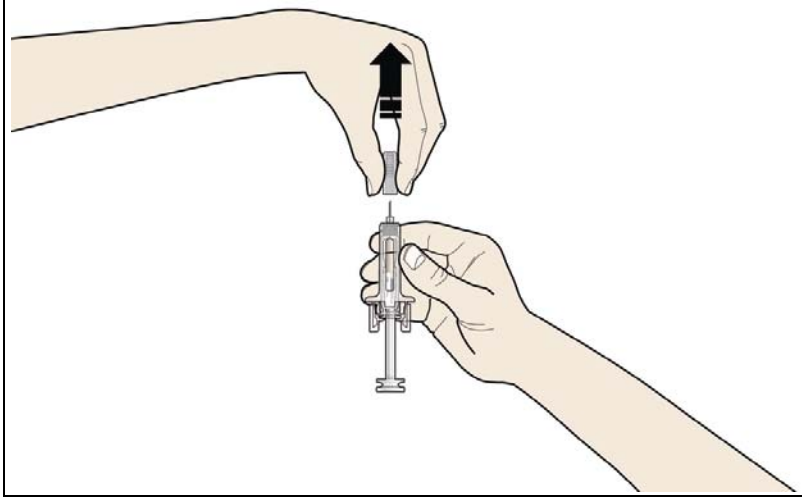
- Upper part of your thigh
- Belly, except for a 5 cm (2-inch) area right around your belly button
- Outer area of upper arm (only if someone else is giving you the injection)

Clean injection site with an alcohol wipe. Let your skin dry.

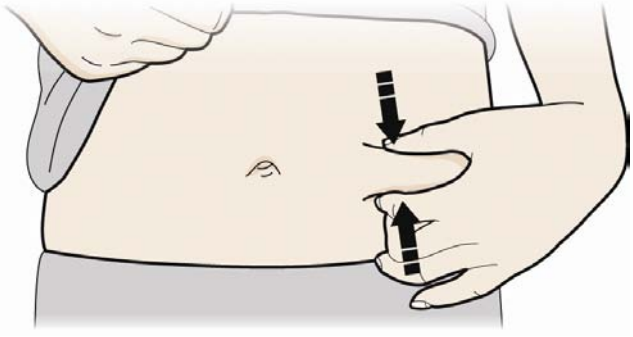
✘ **Do not** touch the injection site before injecting

Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

B	Carefully pull grey needle cap straight out and away from your body.

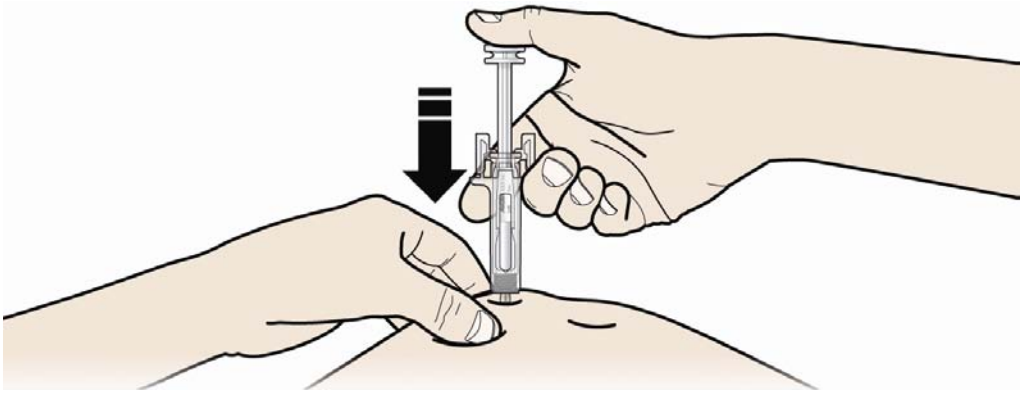


C	Pinch your injection site to create a firm surface.



It is important to keep skin pinched when injecting.

Step 3: Inject	
A	Hold the pinch. INSERT needle into skin.

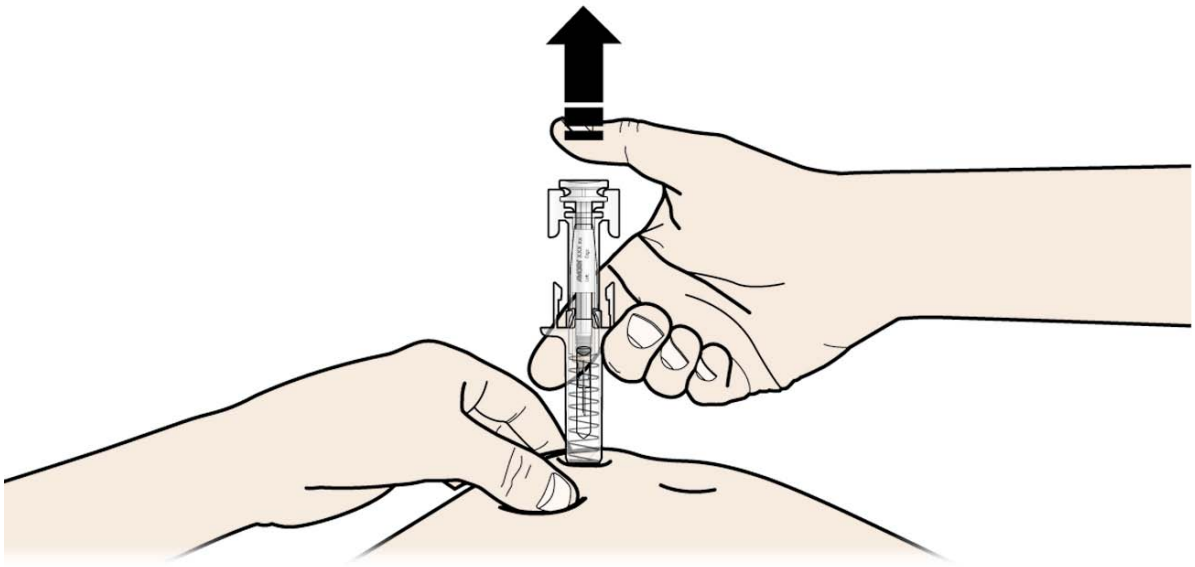


✘ **Do not** touch the cleaned area of the skin

B	PUSH plunger with slow and constant pressure until you feel or hear a “snap”. Push all the way down through the snap.

It’s important to push down through the “snap” to deliver your full dose.

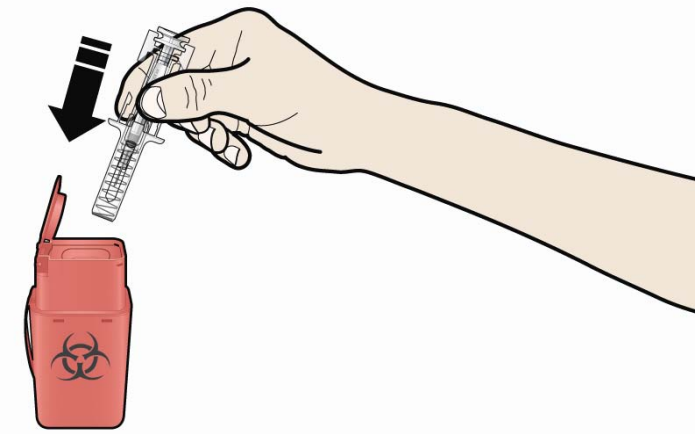
C	RELEASE your thumb. Then LIFT syringe off skin.



After releasing the plunger, the pre-filled syringe safety guard will safely cover the injection needle.

✘ **Do not** put grey needle cap back on used pre-filled syringes.

Step 4: Finish	
A	Discard used pre-filled syringe and other supplies in a sharps disposal container.



Discard used pre-filled syringe and grey needle cap in sharps disposal container. Medicines 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.

Keep syringe and sharps disposal container out of sight and reach of children.

✘ **Do not** reuse pre-filled syringe

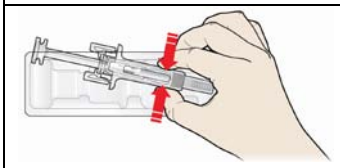
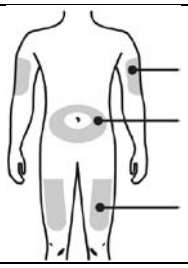
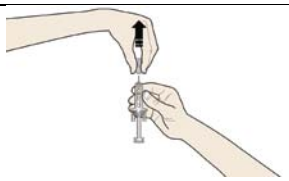
✘ **Do not** recycle pre-filled syringes or throw them into household waste

B	Examine the injection site.

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub injection site. Apply a plaster if needed.

Optional separate additional insert:

Front – Prolia reference guide:

ENGLISH	**Reference Guide** – Read all instructions in carton before use			
	1	2	3	Side 1
	 Grab here	 Upper arm Belly Upper thigh		Turn over to continue…
	Open tray, peeling away cover. Grab pre-filled syringe safety guard to remove pre-filled syringe from tray.	Wash hands thoroughly. Prepare and clean your injection site.	Carefully pull grey needle cap straight out and away from your body.	

Back- Prolia reference guide:

ENGLISH	4	5	6	7	Side 2
					Read other side first
	Hold the pinch. INSERT needle into skin.	PUSH plunger with slow and constant pressure until you feel or hear a "snap". Push all the way down through the snap.	RELEASE your thumb. Then LIFT syringe off skin.	Discard used pre-filled syringe and other supplies in a sharps disposal container.	

Instructions for injecting with the Prolia pre-filled syringe

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.

DO NOT use the pre-filled syringe if the needle cover has been removed.

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.

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 sunlight.

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.

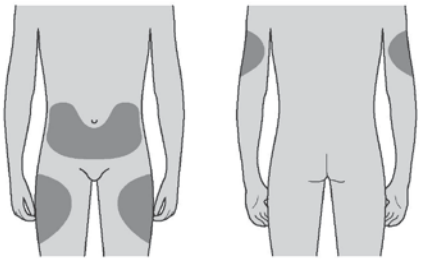
5. Check the expiry date on the pre-filled syringe label (EXP).
   DO NOT use it if the date has passed the last day of the month shown.

6. Check the appearance of Prolia. It must be a clear, colourless to slightly yellow solution. The solution should not be injected if it contains particles or if it is discoloured or cloudy.

7. Find a comfortable, well-lit, clean surface and put all the equipment within reach.

8. Wash your hands thoroughly.

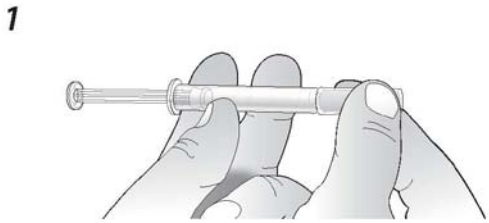
Where should you give the injection?
The best places to inject are the top of your thighs and the abdomen.
Your carer can also use the outer area of your upper arms.



How do you give the injection?

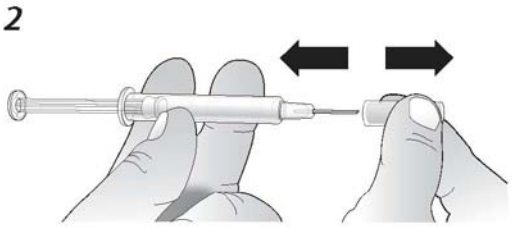
1. Disinfect the skin by using an alcohol wipe.

2. To avoid bending the needle, gently pull the cover from the needle straight off without twisting, as shown in pictures 1 and 2.
DO NOT touch the needle or push the plunger.



3. You may notice a small air 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.**

6. Remove the needle and let go of the skin.

7. 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.

8. 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 cover back on used needles.
- 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.

Package leaflet: Information for the user

Prolia 60 mg solution for injection
denosumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Prolia is and what it is used for

What Prolia is and how it works

Prolia contains denosumab, a protein (monoclonal antibody) that interferes with the action of another protein, in order to treat bone loss and osteoporosis. Treatment with Prolia makes bone stronger and less likely to break.

Bone is a living tissue and is renewed all the time. Oestrogen helps keep bones healthy. After the menopause, oestrogen level drops which may cause bones to become thin and fragile. This can eventually lead to a condition called osteoporosis. Osteoporosis can also occur in men due to a number of causes including ageing and/or a low level of the male hormone, testosterone. Many patients with osteoporosis have no symptoms, but they are still at risk of breaking bones, especially in the spine, hips and wrists.

Surgery or medicines that stop the production of oestrogen or testosterone used to treat patients with breast or prostate cancer can also lead to bone loss. The bones become weaker and break more easily.

What Prolia is used for

Prolia is used to treat:

- osteoporosis in women after the menopause (postmenopausal), reducing the risk of spinal, non-spinal and hip fractures; and osteoporosis in men.
- bone loss that results from a reduction in hormone (testosterone) level caused by surgery or treatment with medicines in patients with prostate cancer.

2. What you need to know before you use Prolia

Do not use Prolia

- if you have low calcium levels in the blood (hypocalcaemia).

- if you are allergic to denosumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before using Prolia

Please tell your doctor immediately if you develop a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), and possibly with symptoms of fever while being on treatment with Prolia.

Tell your doctor if you have or have ever had severe kidney problems, kidney failure or have needed dialysis, which may increase your risk of getting low blood calcium if you do not take calcium supplements.

You should also take calcium and vitamin D supplements while being on treatment with Prolia. Your doctor will discuss this with you.

A dental examination should be considered before you start treatment with Prolia if you have cancer, are undergoing chemotherapy or radiotherapy, are taking steroids, do not receive routine dental care or have gum disease.

If you are under dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Prolia.

It is important to maintain good oral hygiene when being on treatment with Prolia.

Children and adolescents

Prolia is not recommended for children and adolescents under 18 years of age. The use of Prolia in children and adolescents has not been studied.

Other medicines and Prolia

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is especially important that you tell your doctor if you are being treated with another medicine containing denosumab.

You should not take Prolia together with another medicine containing denosumab.

Pregnancy and breast-feeding

Prolia has not been tested in pregnant women. It is important to tell your doctor if you are pregnant; think you may be pregnant; or plan to get pregnant. Prolia is not recommended for use if you are pregnant.

If you become pregnant during Prolia treatment, please inform your doctor. You may be encouraged to enrol in Amgen’s Pregnancy Surveillance programme. Local representative contact details are provided in section 6 of this leaflet.

It is not known whether Prolia is excreted in breast milk. It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Prolia, considering the benefit of breast-feeding to the baby and the benefit of Prolia to the mother.

If you are nursing during Prolia treatment, please inform your doctor. You may be encouraged to enrol in Amgen's Lactation Surveillance Program. Local representative contact details are provided in section 6 of this leaflet.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Prolia has no or negligible influence on the ability to drive and use machines.

Prolia contains sorbitol (E420)

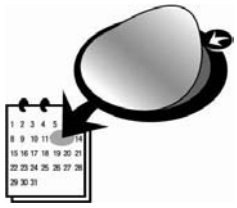
If you have been told by your doctor that you have an intolerance to some sugars (sorbitol E420), contact your doctor before taking this medicinal product.

If you are on a controlled sodium diet

This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg, i.e. essentially 'sodium-free'.

3. How to use Prolia

The recommended dose is one vial of 60 mg administered once every 6 months, as a single injection under the skin (subcutaneous). 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 arm. Each pack of Prolia contains a reminder card with stickers that can be removed from the carton. Use the peel-off stickers to mark the next injection date on your personal calendar and/or the reminder card to keep a record of the next injection date.



You should also take calcium and vitamin D supplements while being on treatment with Prolia. Your doctor will discuss this with you.

Your doctor or healthcare provider will show your carer how to use Prolia.

If you forget to use Prolia

If a dose of Prolia is missed, the injection should be administered as soon as possible. Thereafter, injections should be scheduled every 6 months from the date of the last injection.

If you stop using Prolia

To get the most benefit from your treatment, it is important to use Prolia for as long as your doctor prescribes it for you. Please talk to your doctor before you consider stopping the treatment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Uncommonly, patients receiving Prolia may develop skin infections (predominantly cellulitis). **Please tell your doctor immediately** if you develop any of these symptoms while being on treatment with Prolia: swollen, red area of skin, most commonly in the lower leg, that feels hot and tender, and possibly with symptoms of fever.

Very common side effects (affects more than 1 in 10 people)**:**

- arm or leg pain (pain in extremity).

Common side effects (affects 1 to 10 users in 100):

- painful urination, frequent urination, blood in the urine, inability to hold your urine,
- upper respiratory tract infection,
- pain, tingling or numbness that moves down your leg (sciatica),
- cloudy area in the lens of the eye (cataracts),
- constipation,
- abdominal discomfort,
- rash,
- skin condition with itching, redness and/or dryness (eczema).

Uncommon side effects (affects 1 to 10 users in 1,000):

- fever, vomiting and abdominal pain or discomfort (diverticulitis),
- ear infection.

Rare side effects (affects 1 to 10 users in 10,000):

- persistent pain and/or non-healing sores of the mouth or jaw,
- spasms, twitches, or cramps in your muscles, and/or numbness or tingling in your fingers, toes or around your mouth. These could be signs that you have low calcium levels in the blood (hypocalcaemia),
- allergic reactions (e.g. swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin, wheezing or difficulty breathing).

Unusual fractures of the thigh bone may occur rarely. Contact your doctor if you experience new or unusual pain in your hip, groin or thigh while being on treatment with Prolia as this may be an early indication of a possible fracture of the thigh bone.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Prolia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.
Do not shake excessively.

Your vial may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. Once your vial has been left to reach room temperature (up to 25°C), it must be used within 30 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Prolia contains

- The active substance is denosumab. Each vial contains 60 mg of denosumab in 1 ml of solution (60 mg/ml).
- The other ingredients are acetic acid, glacial, sodium hydroxide, sorbitol (E420) and water for injections.

What Prolia looks like and contents of the pack

Prolia is a clear, colourless to slightly yellow solution for injection provided in a vial. It may contain trace amounts of clear to white particles.

Each pack contains one vial.

Marketing Authorisation Holder and Manufacturer
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder:
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Manufacturer:
Amgen Technology Ireland (ADL)
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Dun Laoghaire
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Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

The following information is intended for healthcare professionals only:

Before administration, the Prolia solution should be inspected visually. The solution may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discoloured. Do not shake excessively. To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25ºC) before injecting and inject slowly. Inject the entire contents of the vial. A 27 gauge needle is recommended for the administration of denosumab. Do not re-enter the vial.

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