

PROLIA™ 60 MG

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).

Patient Card

This product is marketed with patient safety information card (patient card). Please explain to the patient the implications of this treatment including the need for compliance. Please also explain the signs of important adverse events and instruct the patient when to seek medical care .

Patients with renal impairment

No dose adjustment is required in patients with renal impairment (see sections 4.4 for recommendations relating to monitoring of calcium).

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

For subcutaneous use.

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

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.
- Pregnancy:
Prolia may cause fetal harm when administered to a pregnant woman. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. Prolia is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

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

It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment (see section 4.8 for symptoms) calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.

In the post-marketing setting, severe symptomatic hypocalcaemia has been reported (see section 4.8), with most cases occurring in the first weeks of initiating therapy, but it can occur later.

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)

ONJ has been reported rarely in patients receiving Prolia for osteoporosis (see section 4.8).

The start of treatment / new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Prolia in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with Prolia. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Prolia administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

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

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

During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Prolia therapy should be considered, pending a risk/benefit assessment, on an individual basis.

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).

Suppression of Bone Turnover

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

Renal impairment

Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients, see above.

Dry natural rubber

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

Warnings for Excipients

This medicinal product contains sorbitol. 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 medicinal products 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

Prolia may cause fetal harm when administered to a pregnant woman based on findings in animals. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. Prolia is contraindicated in women who are pregnant. If this drug is used during

pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Clinical Considerations

The effects of Prolia on the fetus are likely to be greater during the second and third trimesters of pregnancy. Monoclonal antibodies, such as denosumab, are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. If the patient becomes pregnant during Prolia therapy, treatment should be discontinued and the patient should consult their physician.

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.

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.

The most common side effects with Prolia (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. 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 in patients taking 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each frequency grouping and system organ class, adverse reactions 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 Common Uncommon Uncommon Uncommon	Urinary tract infection Upper respiratory tract infection Diverticulitis ¹ Cellulitis ¹ Ear infection
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 Very common Rare Rare	Pain in extremity Musculoskeletal pain ¹ 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 predominantly reported in patients at increased risk of hypocalcaemia receiving Prolia, with most cases occurring in the first weeks of initiating therapy. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status (see section 4.4). Symptoms of hypocalcaemia in denosumab clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps.

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

ONJ has been reported rarely, in 14 patients, in clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation including a total of 19,521 patients (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.

Musculoskeletal pain

Musculoskeletal pain, including severe cases, has been reported in patients receiving Prolia in the post-marketing setting. In clinical trials, musculoskeletal pain was very common in both denosumab and placebo groups. Musculoskeletal pain leading to discontinuation of study treatment was uncommon.

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 to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@moh.health.gov.il). Additionally, you should also report to GSK Israel, (il.safety@gsk.com).

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 $\geq 87\%$ to approximately $\geq 45\%$ (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 postmenopausal 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 women (2343 Prolia & 2207 placebo) who missed no more than one dose of investigational product in the pivotal study described above and completed the month 36 study visit agreed to enrol in a 7-year, multinational, multicentre, open-label, single-arm extension study to evaluate the long-term safety and efficacy of Prolia. All women in the extension study received Prolia 60 mg every 6 months, as well as daily calcium (at least 1 g) and vitamin D (at least 400 IU). At month 60 of the extension study, after 8 years of Prolia treatment, the long-term group ($n = 1542$) had increased in BMD by 18.4% at the lumbar spine, 8.3% at the total hip, 7.8% at the femoral neck and 11.6% at the trochanter from the original pivotal study baseline. Fracture incidence was evaluated as

a safety endpoint. In years 4 through 8, the rates of new vertebral and non-vertebral fractures did not increase over time; annualised rates were approximately 1.1% and 1.3% respectively.

Eight adjudicated cases of osteonecrosis of the jaw (ONJ) and two atypical fractures of the femur have occurred during the extension study.

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 m² 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. Forty-one women participated in the bone biopsy sub-study at month 24 of the extension study. Bone histology was also evaluated in 17 men with osteoporosis following 1 year treatment with Prolia. Bone biopsy results 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.

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

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

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation.

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

Sorbitol (E420)

glacial Acetic Acid*

Polysorbate 20

Sodium hydroxide (for pH adjustment)*

Water for injection

* 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

The expiry date of the product is indicated on the label and packaging.

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.

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 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.

7. MANUFACTURER

Amgen Europe B.V. Breda, The Netherlands

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

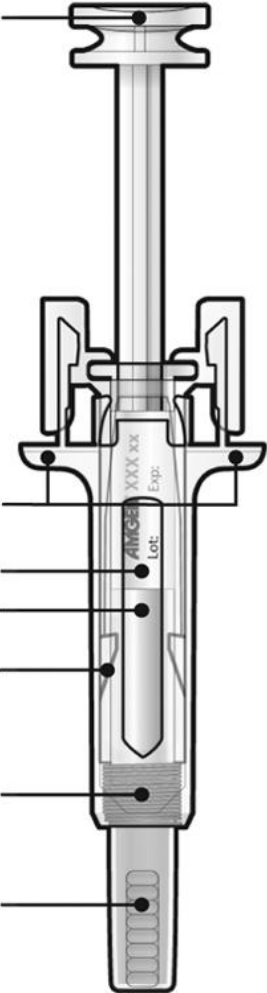
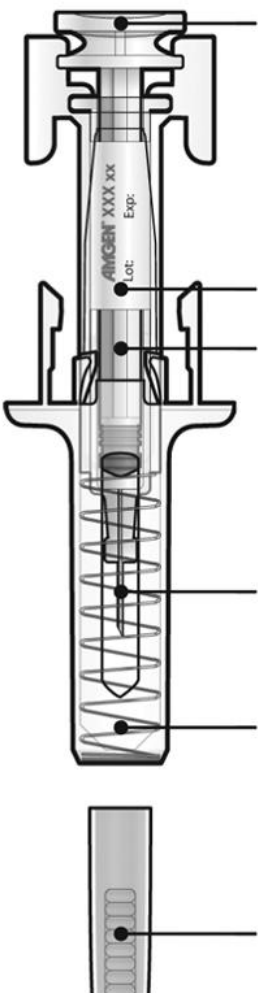
9. LICENCE NUNBER

146-25-33253

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Instructions for use:

Guide to parts	
Before use	After use
<p>Plunger</p>  <p>Finger grips</p> <p>Syringe label</p> <p>Syringe barrel</p> <p>Syringe safety guard</p> <p>Needle safety spring</p> <p>Grey needle cap on</p>	<p>Used plunger</p>  <p>Syringe label</p> <p>Used syringe barrel</p> <p>Used needle</p> <p>Used needle safety spring</p> <p>Grey needle cap off</p>

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 cap on the pre-filled syringe contains a derivative of latex).
- ✗ **Do not** remove the 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

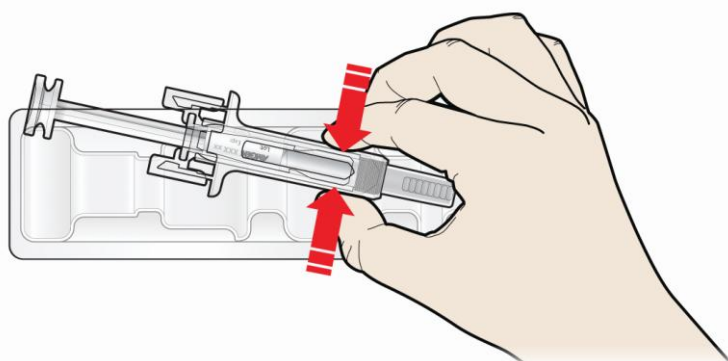
- A Remove the pre-filled syringe tray from the package and gather the supplies needed for your injection: alcohol wipes, a cotton ball or gauze pad, a plaster and a sharps disposal container (not included).

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 and the other supplies.

- ✗ **Do not** try to warm the 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.**

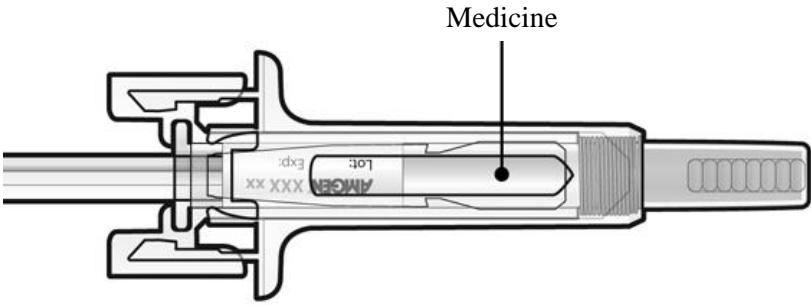
- B Open the tray, peeling away the cover. Grab the pre-filled syringe safety guard to remove the pre-filled syringe from the tray.

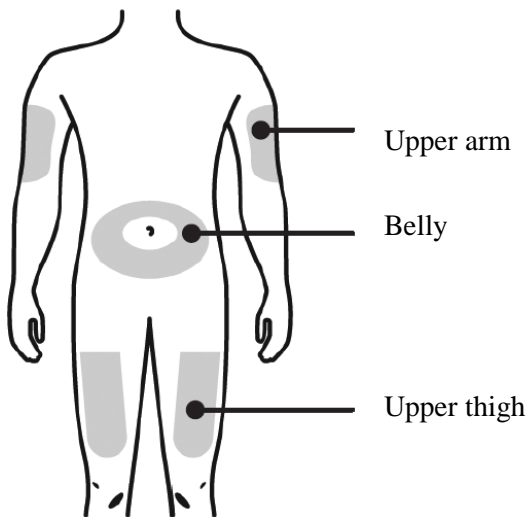


Grab here

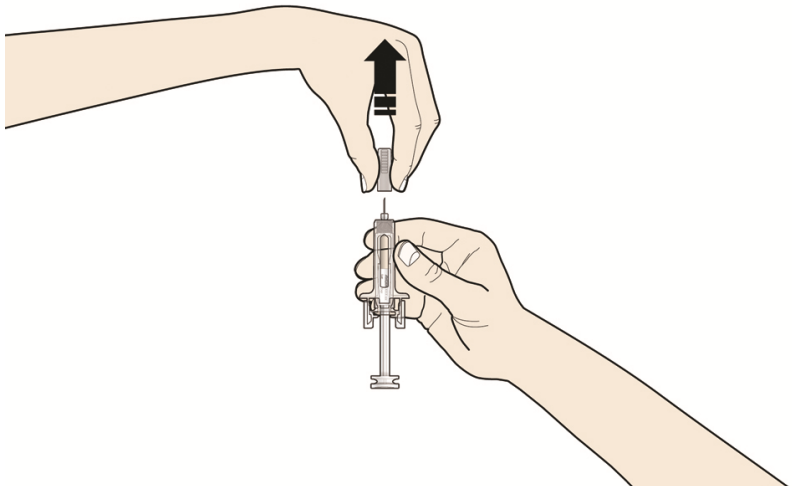
For safety reasons:

- ✗ **Do not** grasp the plunger.
- ✗ **Do not** grasp the grey needle cap.

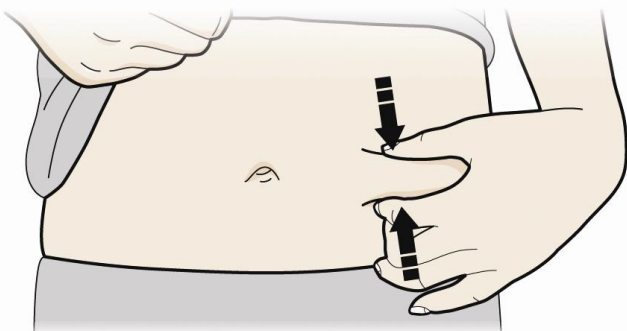
C	Inspect the medicine and pre-filled syringe.
	
<p>✗ Do not use the pre-filled syringe if:</p> <ul style="list-style-type: none"> • The medicine is cloudy or there are particles in it. It must be a clear, colourless to slightly yellow solution. • Any part appears cracked or broken. • The grey needle cap is missing or not securely attached. • The expiry date printed on the label has passed the last day of the month shown. <p>In all cases, call your doctor or healthcare provider.</p>	


Step 2: Get ready	
A	Wash your hands thoroughly. Prepare and clean your injection site.
	
<p>You can use:</p> <ul style="list-style-type: none"> • 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). <p>Clean the injection site with an alcohol wipe. Let your skin dry.</p> <p>✗ Do not touch the injection site before injecting.</p> <p>! Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.</p>	

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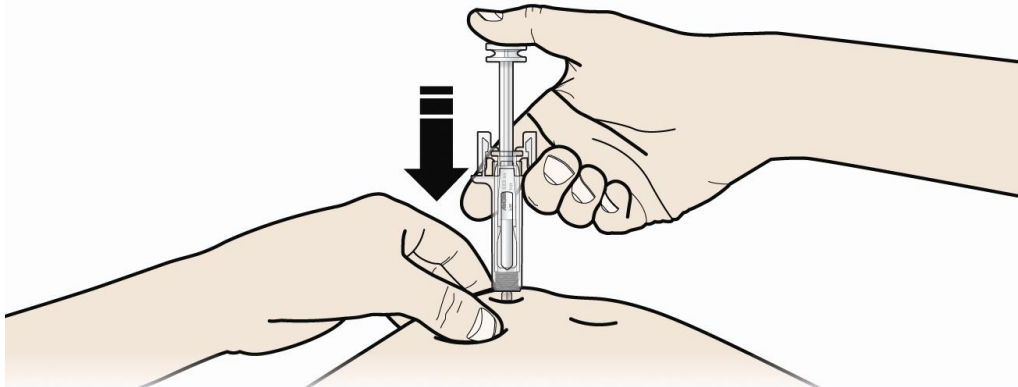


C	Pinch your injection site to create a firm surface.
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 It is important to keep the skin pinched when injecting.

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



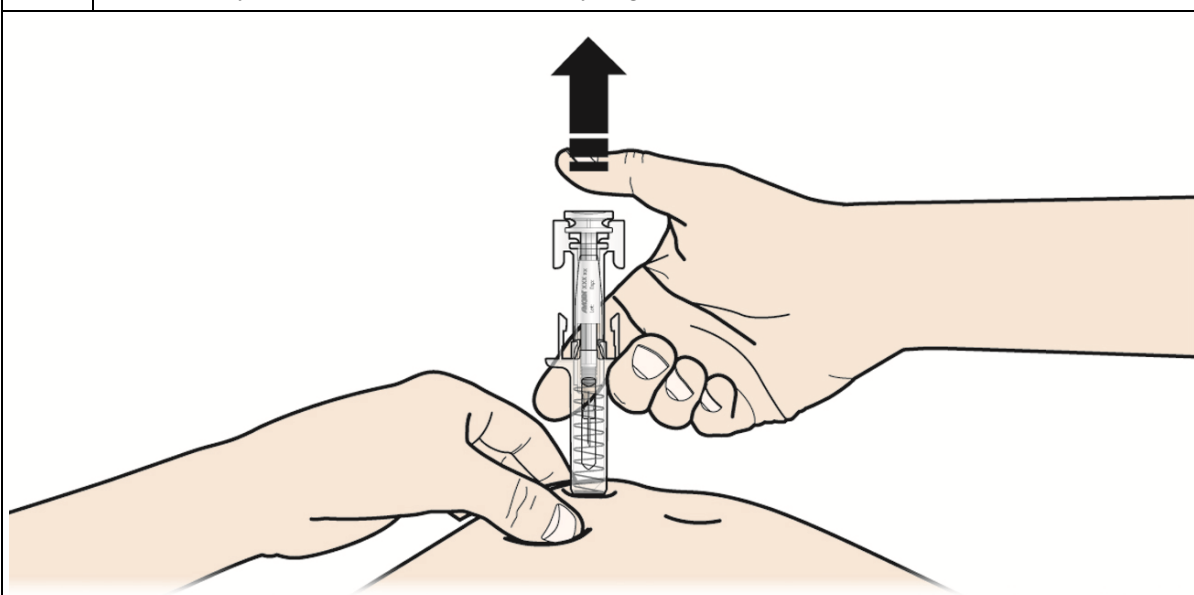
X Do not touch the cleaned area of the skin.

B	PUSH the plunger with slow and constant pressure until you feel or hear a “snap”. Push all the way down through the snap.
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It is important to push down through the “snap” to deliver your full dose.

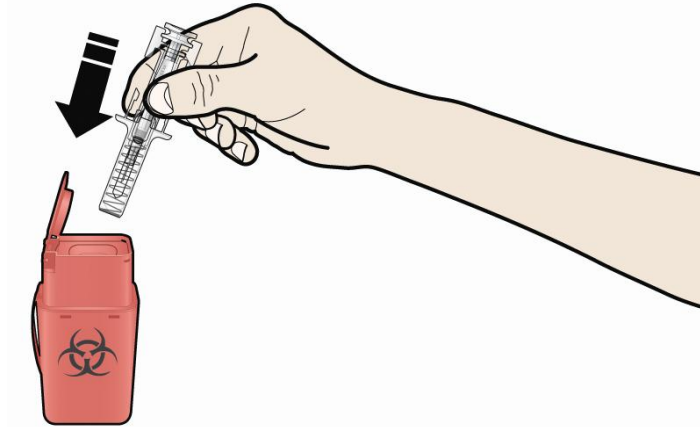
C	RELEASE your thumb. Then LIFT the syringe off skin.
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After releasing the plunger, the pre-filled syringe safety guard will safely cover the injection needle.



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

Step 4: Finish	
A	Discard the used pre-filled syringe and other supplies in a sharps disposal container.
 <p>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.</p> <p>Keep the syringe and sharps disposal container out of sight and reach of children.</p> <ul style="list-style-type: none"> ✗ Do not reuse the pre-filled syringe. ✗ Do not recycle pre-filled syringes or throw them into household waste. 	
B	Examine the injection site.
<p>If there is blood, press a cotton ball or gauze pad on your injection site. Do not rub the injection site. Apply a plaster if needed.</p>	

Pro DR v8