Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) – 1986
The medicine is dispensed according to a doctor's prescription only

Prolia® 60 mg, Solution for subcutaneous injection

Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution.

List of the additional ingredients detailed in section 6.

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the doctor or the pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

In addition to the patient leaflet, Prolia has patient safety information card. This card includes important safety information that you should know before treatment initiation and during the treatment with Prolia and act according to it. The patient safety information card and the patient leaflet should be read prior treatment initiation with this product. The card should be kept for additional reading as needed.

1. What is the medicine intended for?

Prolia is not indicated to be used by children and adolescents under 18 years old.

Prolia is used to treat:
- osteoporosis in women after the menopause (postmenopausal) and men who have an increased risk of fracture (broken bones), reducing the risk of spinal, non-spinal and hip fractures.
- bone loss that results from a reduction in hormone (testosterone) level caused by surgery or treatment with medicines in patients with prostate cancer.
- bone loss associated with long-term systemic glucocorticoids therapy of a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 3 months, in adult patients at high risk of fracture.

Therapeutic group:
Drugs for the treatment of bone disease - other drugs affecting bone structure and mineralization.

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. Estrogen helps keep bones healthy. After the menopause, estrogen 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. It can also occur in patients receiving glucocorticoids. 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 estrogen 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.

2. Before using the medicine

X Do not use the medicine if:

- you have low calcium levels in the blood (hypocalcemia).
- you are sensitive (allergic) to denosumab or to any of the additional ingredients contained in the medicine (listed in section 6).

Special warnings regarding the use of the medicine

Talk to your doctor or pharmacist before using Prolia.

Whilst being treated with Prolia you may develop a skin infection with symptoms such as a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), and possibly with symptoms of fever. Please tell your doctor immediately if you develop any of these symptoms.

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

You may have low levels of calcium in your blood while receiving Prolia. Please tell your doctor immediately if you notice any of the following symptoms: spasms, twitches, or cramps in your muscle, and/or numbness or tingling in your fingers, toes or around your mouth, and/or fits (seizures), confusion, or loss of consciousness.

Severe low blood calcium levels leading to hospitalization and even life-threatening reactions have been reported in rare cases. Before each dose and in patients predisposed to hypocalcemia within two weeks after initial dose, the calcium levels in your blood will therefore be checked (via blood test).

Tell your doctor if you have or have ever had severe kidney problems, kidney failure or have needed dialysis or are taking medicines called glucocorticoids (such as prednisolone or dexamethasone), which may increase your risk of getting low blood calcium if you do not take calcium supplements.

Problems with your mouth, teeth or jaw

A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported rarely (may affect up to 1 in 1,000 people) in patients receiving Prolia for osteoporosis. The risk of ONJ increases in patients treated for a long time (may affect up to 1 in 200 people if treated for 10 years). ONJ can also occur after stopping treatment. It is important to try to prevent ONJ developing as it may be a painful condition that can be difficult to treat. In order to reduce the risk of developing ONJ, take the following precautions:

Before receiving treatment, tell your doctor or nurse (healthcare professional) if:

- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction.
- you don’t receive routine dental care or have not had a dental check-up for a long time.
- you are a smoker (as this may increase the risk of dental problems).
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders).
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone).
- you have cancer.

Your doctor may ask you to undergo a dental examination before you start treatment with Prolia.

While being treated, you should maintain good oral hygiene and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Prolia.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of ONJ.

Unusual thigh bone fractures
Some people have developed unusual fractures in their thigh bone while being treated with Prolia. Contact your doctor if you experience new or unusual pain in your hip, groin, or thigh.

Children and adolescents

Prolia is not indicated for children and adolescents under 18 years of age.

Other medicines and Prolia

If you are taking, have recently taken or might take any other medicines including non-prescription medicines and food supplements, tell the doctor or the pharmacist. 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. Women of child-bearing potential should use effective methods of contraception while being treated with Prolia and for at least 5 months after stopping treatment with Prolia.

If you become pregnant during treatment with Prolia or less than 5 months after stopping treatment with Prolia, please inform your doctor.

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 breast-feeding during Prolia treatment, please inform your doctor.

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.

Important information about some ingredients of the medicine

Prolia contains sorbitol

This medicine contains 47 mg sorbitol in each mL of solution.

Prolia contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 60 mg, that is to say essentially ‘sodium-free’.

3. How should you use the medicine?

Always use this medicine according to the doctor's instructions.

You should check with the doctor or the pharmacist if you are not sure about the dosage and treatment regimen.

The dosage and treatment regimen will be determined by the attending doctor only.

The usual recommended dosage 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.

Please consult your doctor on the date for a potential next injection. Each pack of Prolia contains a reminder card, that can be removed from the carton and used 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.

Do not exceed the recommended dose

Prolia should be administered under the responsibility of a healthcare professional.

If you accidentally have taken a higher dosage

If you have taken an overdose or if a child has accidentally swallowed the medicine, refer immediately to a doctor or to a hospital emergency room and bring the package of the medicine with you.

If you forget to take the medicine

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.

Adhere to the treatment as recommended by the doctor.

If you stop using Prolia

To get the most benefit from your treatment in reducing the risk of fractures, it is important to use Prolia for as long as your doctor prescribes it for you. Do not stop your treatment without contacting your doctor.

Stopping the Prolia treatment can increase the risk of broken bones in the spine, especially in patients with a background of broken bones in the spine. Do not stop taking Prolia without first talking with your doctor. If your Prolia treatment is stopped, discuss other available treatment options with your doctor.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Side effects

As with any medicine, use of Prolia may cause side effects in some of the users. Do not be alarmed by reading the list of side effects. You may not experience any of 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.

Rarely, patients receiving Prolia may develop pain in the mouth and/or jaw, swelling or non-healing of sores in the mouth or jaw, discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis). **Tell your doctor and dentist immediately** if you experience such symptoms while being treated with Prolia or after stopping treatment.

Rarely, patients receiving Prolia may have low calcium levels in the blood (hypocalcemia); severely low blood calcium levels may lead to hospitalization and may even be life-threatening. Symptoms include spasms, twitches, or cramps in your muscles, and/or numbness or tingling in your fingers, toes or around your mouth and/or seizures, confusion, or loss of consciousness. If any of these apply to you, **tell your doctor immediately**. Low calcium in the blood may also lead to a change in heart rhythm called QT prolongation which is seen by electrocardiogram (ECG).

Rarely unusual fractures of the thigh bone may occur in patients receiving Prolia. **Contact your doctor** if you experience new or unusual pain in your hip, groin or thigh as this may be an early indication of a possible fracture of the thigh bone.

Rarely, allergic reactions may occur in patients receiving Prolia. Symptoms include swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin, wheezing or difficulty breathing. **Please tell your doctor** if you develop any of these symptoms while being treated with Prolia.

Very common side effects (may affect more than 1 in 10 people):
- bone, joint, and/or muscle pain which is sometimes severe,
- arm or leg pain (pain in extremity).

Common side effects (may affect up to 1 in 10 people):
- 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),
- constipation,
- abdominal discomfort,
- rash,
- skin condition with itching, redness and/or dryness (eczema),
- hair loss (alopecia).

Uncommon side effects (may affect up to 1 in 100 people):
- fever, vomiting and abdominal pain or discomfort (diverticulitis),
- ear infection,
- rash that may occur on the skin or sores in the mouth (lichenoid drug eruptions),
- broken bones in the spine after stopping Prolia (multiple vertebral fractures).

Very rare side effects (may affect up to 1 in 10,000 people):
- allergic reaction that can damage blood vessels mainly in the skin (e.g. purple or brownish-red spots, hives or skin sores) (hypersensitivity vasculitis).

Not known (frequency cannot be estimated from the available data):
- talk to your doctor if you have ear pain, discharge from the ear and/or an ear infection. These could be signs of bone damage in the ear,
- severe allergic reaction (drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome) with skin rash/blisters, fever and/or increase in a type of white blood cell (eosinophils) with possible organ damage, such as liver, kidney, or lung.

If a side effect has appeared, if any of the side effects get worse or when you suffer from a side effect that has not been mentioned in the leaflet, you should consult the doctor.

Reporting of side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Reporting of Side Effects due to Medical Treatment" located on the Ministry of Health homepage **www.health.gov.il** which directs you to the online form for reporting side effects, or by entering the link: **https://sideeffects.health.gov.il**

5. How to store the medicine?

Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the sight and reach of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.

Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C–8°C).
Do not freeze.
Keep the pre-filled syringe in the original outer carton in order to protect from light.
Do not shake.

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. Additional information

In addition to the active ingredient the medicine also contains:
sorbitol (E420), glacial acetic acid, polysorbate 20, sodium hydroxide, water for injection.

What does the medicine look like and what is the content of the package:

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

Each pack contains one pre-filled syringe with or without automatic needle guard.

Not all pack types may be marketed.

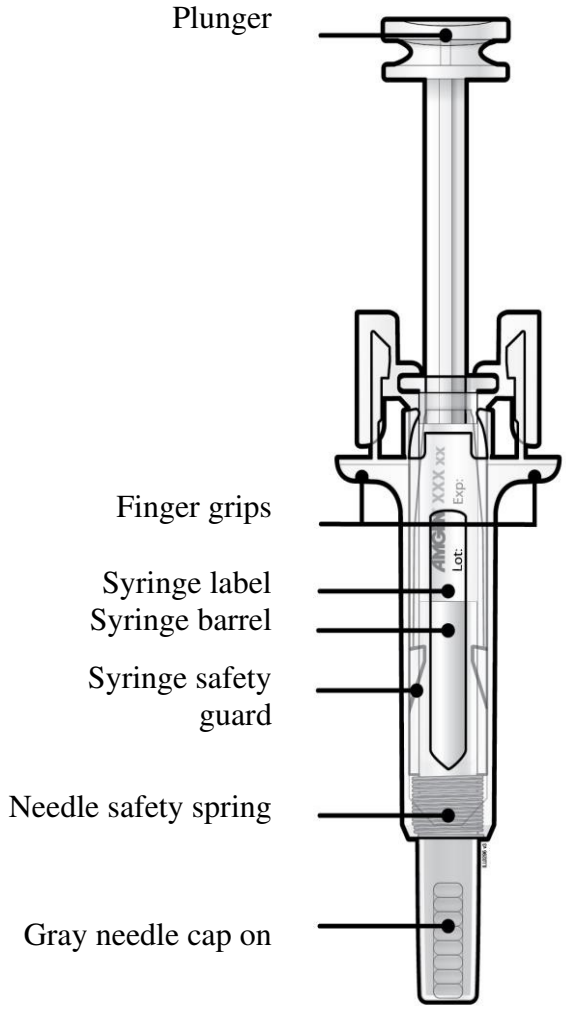
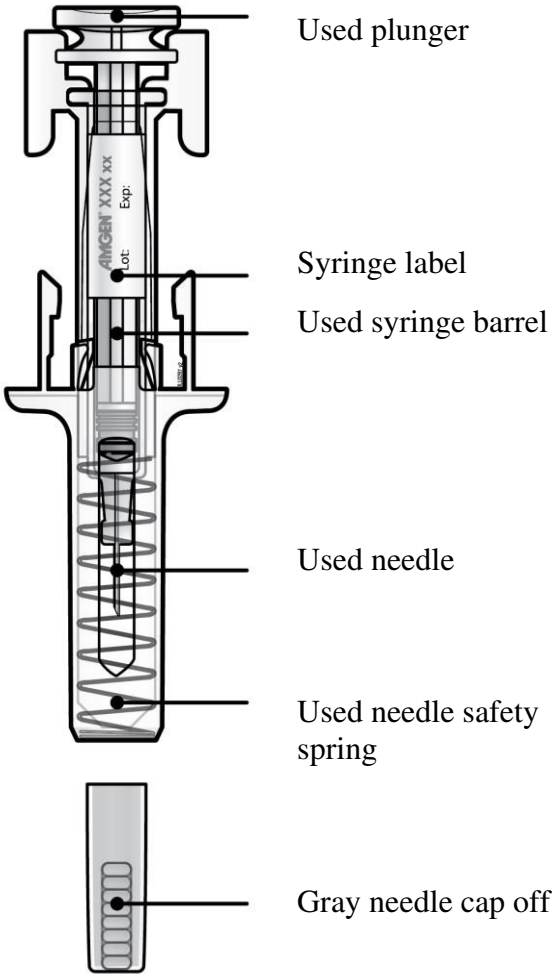
Manufacturer:
Amgen Europe B.V., Minervum 7061, Breda, The Netherlands.

License Holder:
Amgen Europe B.V., P.O. BOX 53313, Tel - Aviv.

Revised in February 2024 according to MoHs guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 146-25-33253

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). ✘ **Do not** remove the gray 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.

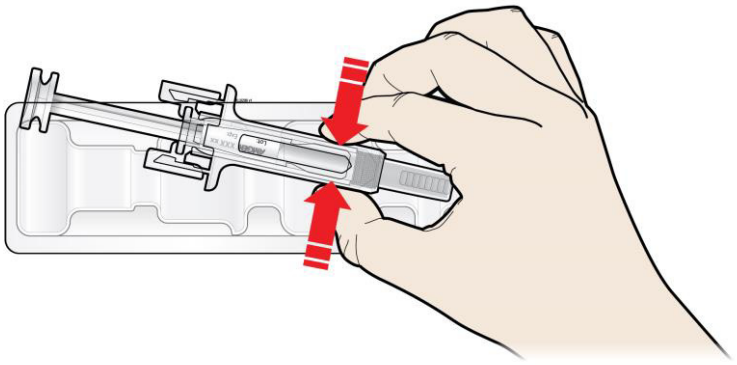
Step 1: **Prepare**	
A	Remove the pre-filled syringe tray from the package and gather the supplies needed for your injection: alcohol wipes, a cotton ball or gauze pad, a plaster and a sharps disposal container (not included).

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.
- • **the pre-filled syringe 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.



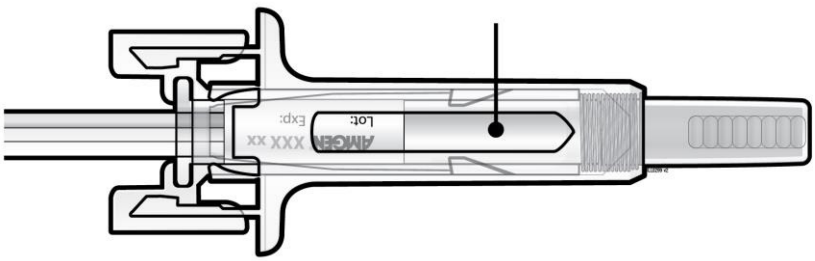
Grab here

For safety reasons:

- ✘ **Do not** grasp the plunger.
- ✘ **Do not** grasp the gray needle cap.

C	Inspect the medicine and pre-filled syringe.

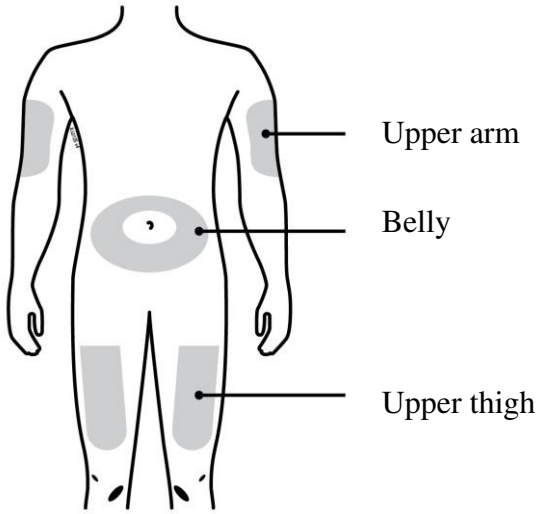
Medicine



- ✘ **Do not** use the pre-filled syringe if:
  - The medicine is cloudy or there are particles in it. It must be a clear, colorless to slightly yellow solution.
  - Any part appears cracked or broken.
  - The gray 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 your hands thoroughly. Prepare and clean your injection site.



You can use:

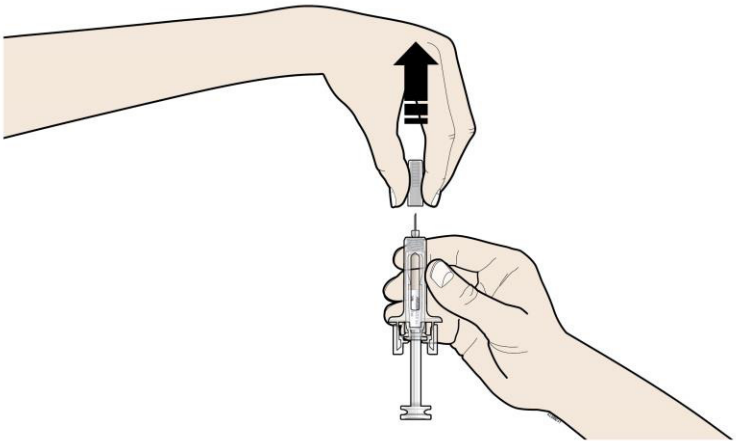
- Upper part of your thigh.
- Belly, except for a 5 cm (2-inch) area right around your belly button.
- Outer area of upper arm (only if someone else is giving you the injection).

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

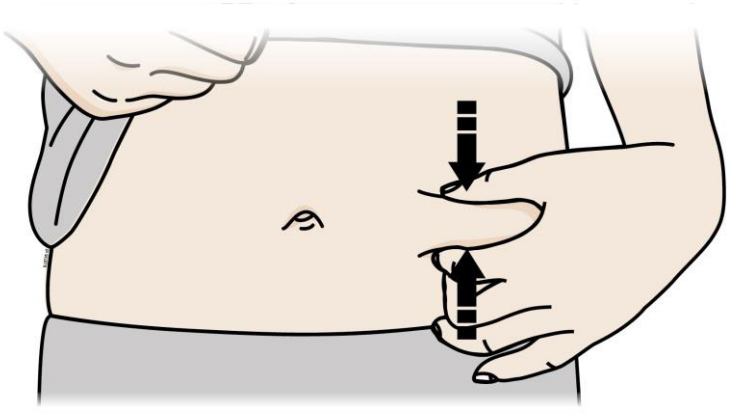
✘ **Do not** touch the injection site before injecting.

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 the gray needle cap straight out and away from your body.

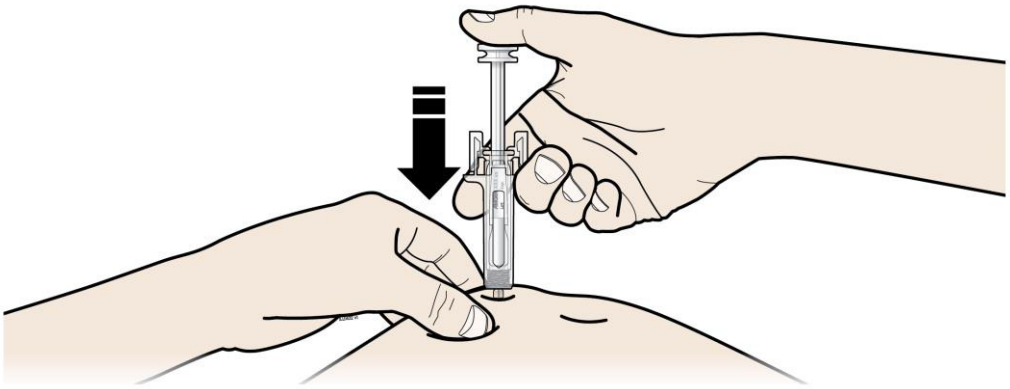


C	Pinch your injection site to create a firm surface.



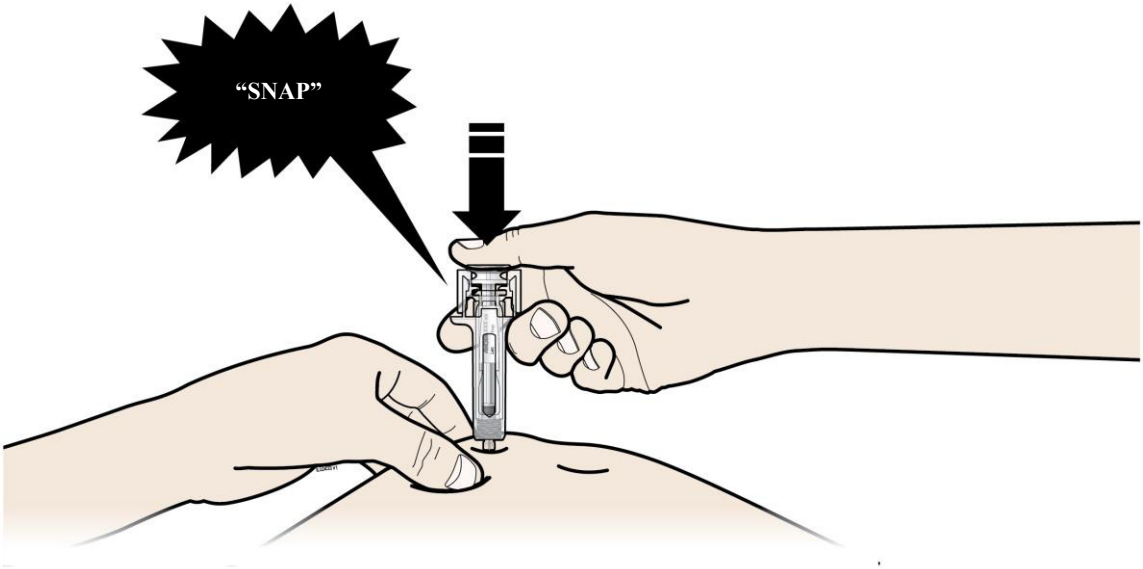
It is important to keep the skin pinched when injecting.

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



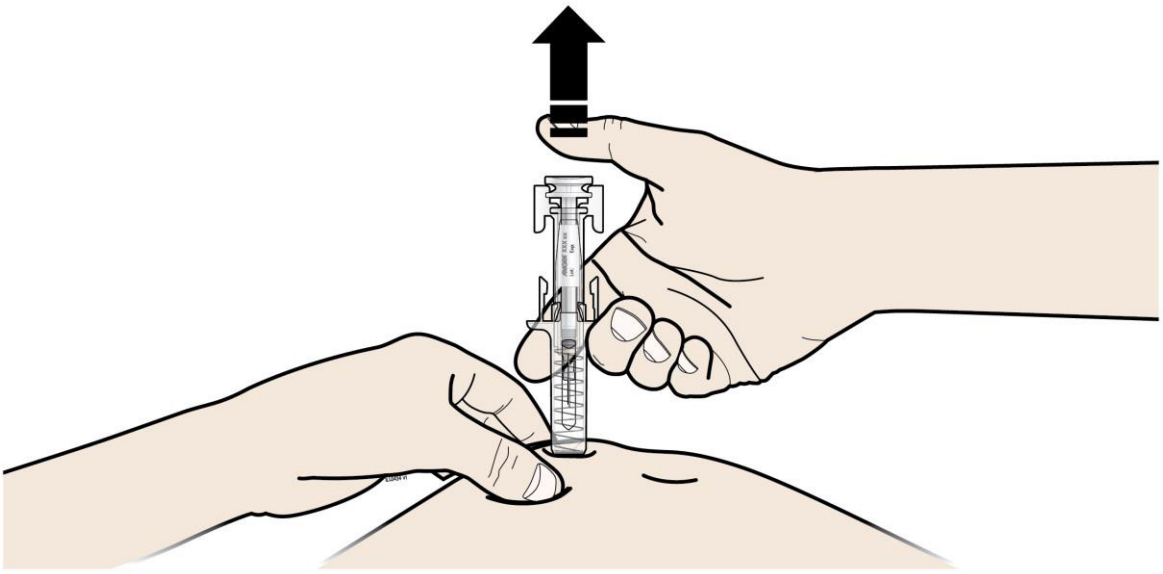
✘ **Do not** touch the cleaned area of the skin.

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



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

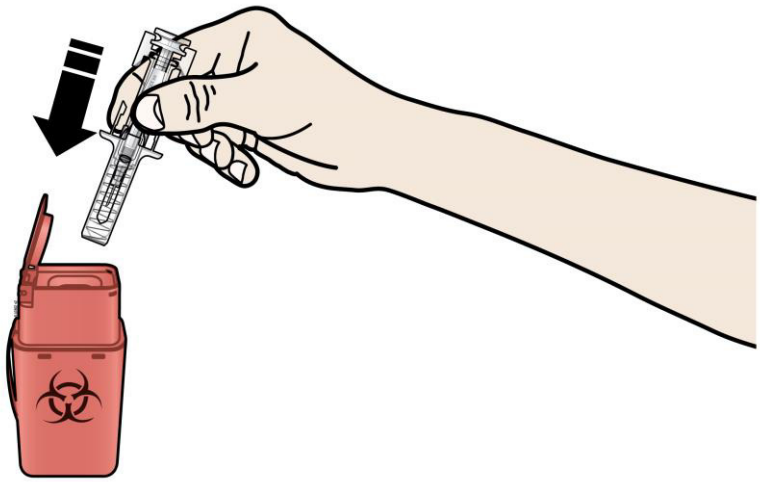
C	RELEASE your thumb. Then LIFT the syringe off skin.



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

✘ **Do not** put the gray 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.



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

✘ **Do not** reuse the 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 the injection site. Apply a plaster if needed.