Patient leaflet in accordance with the Pharmacists' Regulation (Preparations) – 1986

This medicine is dispensed with a doctor's prescription only.

Aranesp® Solution for injection in a pre-filled syringe 20 mcg, 30 mcg, 40 mcg, 50 mcg, 60 mcg, 80 mcg, 100 mcg, 150 mcg, 300 mcg, 500 mcg

Active Ingredient
Each pre-filled syringe of Aranesp 20 mcg, contains 20 mcg of darbepoetin alfa in 0.5 mL (40 mcg/1 mL)
Each pre-filled syringe of Aranesp 30 mcg, contains 30 mcg of darbepoetin alfa in 0.3 mL (100 mcg/1 mL)
Each pre-filled syringe of Aranesp 40 mcg, contains 40 mcg of darbepoetin alfa in 0.4 mL (100 mcg/1 mL)
Each pre-filled syringe of Aranesp 50 mcg, contains 50 mcg of darbepoetin alfa in 0.5 mL (100 mcg/1 mL)
Each pre-filled syringe of Aranesp 60 mcg, contains 60 mcg of darbepoetin alfa in 0.3 mL (200 mcg/1 mL)
Each pre-filled syringe of Aranesp 80 mcg, contains 80 mcg of darbepoetin alfa in 0.4 mL (200 mcg/1 mL)
Each pre-filled syringe of Aranesp 100 mcg, contains 100 mcg of darbepoetin alfa in 0.5 mL (200 mcg/1 mL)
Each pre-filled syringe of Aranesp 150 mcg, contains 150 mcg of darbepoetin alfa in 0.3 mL (500 mcg/1 mL)
Each pre-filled syringe of Aranesp 300 mcg, contains 300 mcg of darbepoetin alfa in 0.6 mL (500 mcg/1 mL)
Each pre-filled syringe of Aranesp 500 mcg, contains 500 mcg of darbepoetin alfa in 1 mL (500 mcg/1 mL)

For Inactive ingredients and allergens in the medicine – see section 6 "Additional information'' Read this leaflet carefully and until the end before using this medicine. This leaflet contains essential information about the medicine. If you have any additional questions, contact your doctor or pharmacist.

This medicine is prescribed for treating your specific illness. Do not pass it on to others. It may cause them harm even if it appears to you that their illness is the same.

1. What is this medicine intended for?

Aranesp is registered for the treatment of anemia. Anemia is a condition where the blood does not contain a sufficient amount of red blood cells, the symptoms may be fatigue, weakness and shortness of breath.

Aranesp works in exactly the same way as the natural hormone erythropoietin. Erythropoietin is produced in the kidneys and encourages bone marrow to produce more red blood cells. The active substance in Aranesp, darbepoetin alfa, is produced by gene technology in Chinese Hamster Ovary Cells.

If you have chronic renal failure
Aranesp is used to treat symptomatic anemia that is associated with chronic renal failure (kidney failure) in adults and children age 1 and over. In kidney failure, the kidney does not produce enough of the natural hormone erythropoietin which can often cause anemia.

Because it will take your body some time to make more red blood cells, it will be about four weeks before you notice any effect. Your normal dialysis routine will not affect the ability of Aranesp to treat your anemia.

If you are receiving chemotherapy
Aranesp dosage of 150, 300, 500 mcg, is used to treat symptomatic anemia in adult cancer patients with non-bone marrow cancers (non-myeloid malignancies) who are receiving chemotherapy.

One of the main side effects of chemotherapy is that it stops the bone marrow producing enough blood cells. At first, only white blood cells seem to be affected. This is because the red blood cells have a much longer life span in the circulating blood. Towards the end of your chemotherapy course, particularly if you have had a lot of chemotherapy, your red blood cell count may fall making you anemic.

Therapeutic Group: Aranesp is an antianemic agent.

2. Before using this medicine

X Don't use this medicine if:
- you are sensitive (allergic) to the active material or to any of the other ingredients in this medicine.
- you have high blood pressure which is not being controlled by the medicines your doctor has prescribed to you.

! Special warnings regarding the usage of the medicine:
! Before treatment with Aranesp, tell the doctor if you have or have ever had:
- **high blood pressure** which is being controlled by the medicines that your doctor has prescribed to you
- **sickle cell anemia**
- **seizures** (epileptic fits)
- **convulsions** (fits or seizures)
- **liver disease**
- **lack of a significant response** to previous medication that you have been given for the treatment of anemia
- an **allergy to latex** (the needle cap on the pre-filled syringe contains a derivative of latex), or
- hepatitis C.

If you are sensitive to any food product or medicines, you must inform your physician before taking this drug.

- If you have symptoms which include unusual tiredness and a lack of energy this could mean you have pure red cell aplasia (PRCA), which has been reported in patients. PRCA means that the body has stopped or reduced the production of red blood cells which causes severe anemia. If you experience these symptoms you should contact your doctor who will determine the best course of action to treat your anemia.

- Take special care with other products that stimulate red blood cell production: Aranesp is one of a group of products that stimulate the production of red blood cells like the human protein erythropoietin does. Your healthcare professional should always record the exact product you are using.

- If you are a patient with chronic renal failure, and particularly if you do not respond properly to Aranesp, your doctor will check your dose of Aranesp because repeatedly increasing your dose of Aranesp if you are not responding to treatment may increase the risk of having a problem of the heart or the blood vessels and could increase risk of myocardial infarction, stroke and death.

- Your doctor should try to keep your hemoglobin between 10 and 12 g/dL. Your doctor will check that your hemoglobin does not exceed a certain level, as high hemoglobin concentrations could put you at risk of having a problem of the heart or the blood vessels and could increase risk of myocardial infarction, stroke and death.

- If you have symptoms which include severe headache, drowsiness, confusion, problems with your eyesight, nausea, vomiting or fits (seizures), it could mean that you have very high blood pressure. If you experience these symptoms you should contact your doctor.

- If you are a cancer patient you should be aware that Aranesp may act as a blood cell growth factor and in some circumstances may have a negative impact on your cancer. Depending on your individual situation a blood transfusion may be preferable. Please discuss this with your doctor.

- Misuse by healthy people can cause life-threatening problems with the heart or blood vessels.

- Serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with epoetin treatment. SJS/TEN can appear initially as reddish target-like spots or circular patches often with central blisters on the trunk. Also, ulcers of mouth, throat, nose, genitals and eyes (red and swollen eyes) can occur. These serious skin rashes are often preceded by fever and/or flu-like symptoms. The rashes may progress to widespread peeling of the skin and life-threatening complications.
  If you develop a serious rash or another of these skin symptoms, stop taking Aranesp and contact your doctor or seek medical attention immediately.

If you are taking other medicines, including non-prescription medicines and food supplements, tell the doctor or pharmacist. In particular, you should inform the doctor or pharmacist if you are taking:

Cyclosporin and tacrolimus which may be affected by the number of red cells in your blood. It is important to tell your doctor if you are taking either of these drugs.

Pregnancy and breast-feeding
Consult the doctor or pharmacist before using the medicine.

Aranesp has not been tested in pregnant women, it is important to let your doctor know if you are pregnant, may be pregnant or planning a pregnancy. It is unknown whether darbepoetin alfa is secreted to maternal milk. Breast-feeding must be stopped if you are being treated with Aranesp.

Driving and using machines
Aranesp should not affect your ability to drive or use machinery.

Aranesp contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to Use This Medicine

Always use this medicine in accordance with a doctor's instructions.

Check with a doctor or a pharmacist if you are not sure.

Dosage and treatment will be determined by the doctor only. Do not exceed the recommended dosage.

The recommended dosage is usually:

If you have chronic renal failure
For all adult and pediatric patients ≥ 1 year of age with chronic renal failure, Aranesp is administered as a single injection, either under your skin (by subcutaneous injection) or into a vein (intravenous).

In order to correct the anemia, the initial dose of Aranesp per body kilogram, will be as follows:
- 0.75 mcg once every 2 weeks or
- 0.45 mcg once a week.

For adult patients not on dialysis, 1.5 mcg/kg once monthly may also be used as the initial dose.

For all adult and pediatric patients ≥ 1 year of age with chronic renal failure, once your anemia is corrected you will continue to receive Aranesp given as a single injection, either once a week or once every two weeks. If you are over 18 years and not on dialysis, Aranesp could also be given as an injection once monthly.

The physician will perform blood tests regularly to determine how the anemia is responding. The physician may adjust the dose once every 4 weeks, if needed in order to maintain long-term control of your anemia.

Your doctor will use the lowest effective dose to control the symptoms of your anemia.

If you do not respond adequately to Aranesp, your doctor will check your dose and will inform you if you need to change doses of Aranesp.

Your blood pressure will also regularly be tested, especially in the beginning of treatment.

In certain cases your doctor may recommend iron supplement.

Your physician may decide to change the way the injection is given (subcutaneous or intravenous). If the doctor changes the way you inject, you must start with the same dose. The physician must continue to monitor your blood tests to make sure that the anemia is still under control.

If your physician has switched you from treatment with r-HuEPO (erythropoietin produced by genetic

technology) to Aranesp he must decide whether Aranesp must be administered once a week or once every two weeks. The way you inject Aranesp will be similar to the way you inject r-HuEPO, but your physician will guide you regarding the dose and the duration of injection. He may also adjust the dose if necessary.

If you are receiving chemotherapy
Aranesp is given as a single injection for adults, either once a week or once every three weeks, under your skin.

In order to correct the anemia, the initial dose will be:
- 500 mcg once every 3 weeks (6.75 mcg of Aranesp for each kilogram body weight), or
- 2.25 mcg once a week of Aranesp for each kilogram body weight.

Your doctor will perform blood tests on a regular basis to determine whether the anemia is responding and may adjust the dose if needed. The duration of therapy will last for about 4 weeks after you finish your chemotherapy. The physician will instruct you when exactly you should stop taking Aranesp.

In some cases your doctor may recommend that you take an iron supplement.

Instructions for Injection:
Your doctor will decide on the need for treatment with Aranesp, if your hemoglobin level is 10 g/dL or less. Your physician will guide you regarding the dose and how frequently you must inject Aranesp in order to maintain your hemoglobin level between 10 – 12 g/dL.

Self Injection of Aranesp:
Your physician has decided that the Aranesp pre-filled syringe is the best way for you, a nurse, or a care taker to inject Aranesp. The attending physician, nurse or pharmacist will demonstrate how to perform self injections by using Aranesp pre-filled syringe. Do not try to self inject unless you have received an instruction. **Never inject Aranesp into a vein yourself!**

If you accidentally took a higher dose you could have serious problems, such as very high blood pressure. You should contact your doctor, nurse or pharmacist if this does happen. If you feel unwell in any way you should contact your doctor, nurse or pharmacist immediately.

If you forgot to take the medicine do not use a double dose to make up for a forgotten one.

If you have forgotten a dose of Aranesp, you should contact your doctor to discuss when you should inject the next dose.

Treatment should persist in accordance with the doctor's recommendations.

If you stop treatment with the medicine
If you want to stop using Aranesp, you should discuss it with your doctor first.

If you have any additional questions regarding the usage of this medicine, consult a doctor or a pharmacist.

How can you help to make this treatment more successful?
Complete the treatment as recommended by the attending physician.
Even if you feel an improvement in your health, do not stop taking this medicine without consulting your physician.

Don't take medicines in the dark! Check the label and dosage every time that you take medicine. Put on your glasses if you need them.

4. Side Effects

Like any medicine, using Aranesp may cause side effects in some of the users. Do not be afraid of reading the list of side effects. It is possible that you will not suffer from any one of them.

Chronic renal failure patients

Very common: may affect more than 1 in 10 people
- High blood pressure (hypertension)
- Allergic reactions

Common: may affect up to 1 in 10 people
- Stroke
- Pain around the injection site
- Rash and/or redness of the skin

Uncommon: may affect up to 1 in 100 people
- Blood clots (thrombosis)
- Convulsions (fits and seizures)
- Bruising and bleeding at the site of injection
- Blood clots in a dialysis access

Not known: frequency cannot be estimated from available data
- Pure red cell aplasia (PRCA) – (anemia, unusual tiredness, lack of energy)

Cancer patients

Very common: may affect more than 1 in 10 people
- Allergic reactions

Common: may affect up to 1 in 10 people
- High blood pressure (hypertension)
- Blood clots (thrombosis)
- Pain around the area injected
- Rash and/or redness of the skin
- Fluid retention (edema)

Uncommon: may affect up to 1 in 100 people
- Convulsions (fits and seizures)
- Bruising and bleeding at the site of injection

All patients

Not known: frequency cannot be estimated from available data
- Serious allergic reactions which may include:
  - Sudden life-threatening allergic reactions (anaphylaxis)
  - Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema)
  - Shortness of breath (allergic bronchospasm)
  - Skin rash
  - Hives (urticaria)
- Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with epoetin treatment. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms.
  Stop using Aranesp if you develop these symptoms and contact your doctor or seek medical attention immediately (see section 2 “Before using this medicine”).

If a side effect occurs, if one of the side effects gets worse, or when you suffer from a side effect that is not mentioned in the leaflet, consult with the doctor.

Side effects and drug interactions in children:
Parents should report any side effects and additional medicines that are given to the child to the attending physician. See side effects and drug interactions as mentioned above.

Pay Attention:
This medicine is intended for subcutaneous or intravenous injection.

This medicine is intended for use in adults and children above the age of 1 year treated for chronic renal failure, and for adults only receiving chemotherapy.

Reporting of side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage **www.health.gov.il** that 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 toxicity! This medicine and any other medicine should be stored in a closed place, out of the reach of children and/or infants, thereby preventing toxicity. Do not cause vomiting without an explicit instruction from a doctor.
- Don't use this medicine after the expiry date (EXP) that appears on the package and blister. The expiry date refers to the last day of that particular month.
- Keep in the original package to protect from light.
- Must be stored in a refrigerator (2°C-8°C).
- Do not freeze. Do not use Aranesp if you think it may have been frozen.
- When your syringe has been removed from the refrigerator and left at room temperature for approximately 30 minutes before injection, it must either be used within 7 days or disposed of.
- Aranesp is a clear, colorless or slightly pearly liquid. If it is cloudy or there are particles in it, you must not use it.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Additional Information

In addition to the active ingredient, this medicine also contains:
- Sodium phosphate monobasic (2.12 mg/mL)
- Sodium phosphate dibasic (0.66 mg/mL)
- Sodium chloride (8.18 mg/mL)
- Polysorbate 80 (0.05 mg/mL)
- Water for injections

How the medicine looks and what is the content of the package?
Aranesp is a clear, colorless or slightly pearly liquid. If it is cloudy or there are particles in it, you must not use it.

Aranesp is packaged in 1 or 4 ready to use pre-filled syringes with automatic needle guard in a blister wrapping, not all packages are being marketed.

Registration Holder's name and address:
Amgen Europe B.V., P.O. BOX 53313, Tel - Aviv.

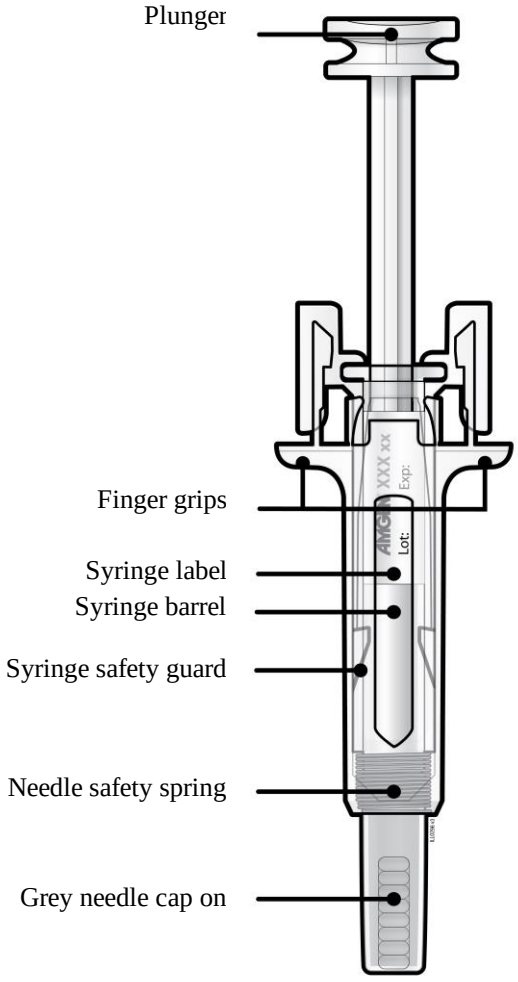
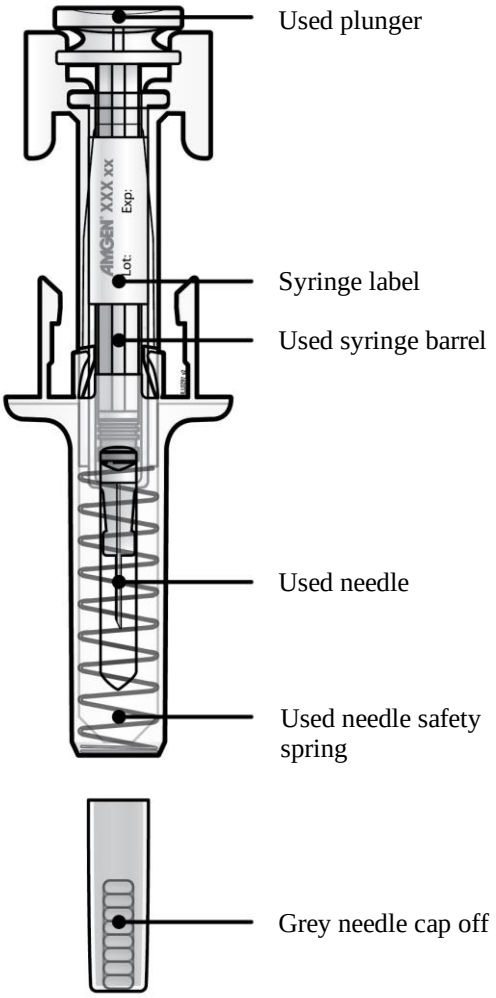
Manufacturer's name and address:
Amgen Europe B.V., Minervum 7061, Breda, The Netherlands.

Revised in March 2021 according to MoHs guidelines.

Registration number of the medicine in the National Drugs Registry at the Ministry of Health:

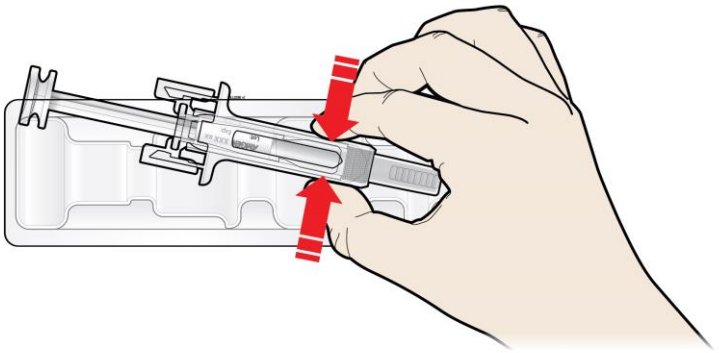
Aranesp 10 mcg: 124 38 30392
Aranesp 20 mcg: 124 40 30394
Aranesp 30 mcg: 124 41 30395
Aranesp 40 mcg: 124 42 30396
Aranesp 50 mcg: 124 43 30397
Aranesp 60 mcg: 124 44 30398
Aranesp 80 mcg: 124 45 30399
Aranesp 100 mcg: 124 46 30400
Aranesp 150 mcg: 124 47 30401
Aranesp 300 mcg: 129 65 30888
Aranesp 500 mcg: 133 32 31237

Instructions for use:

Guide to parts	
Before use	After use
	

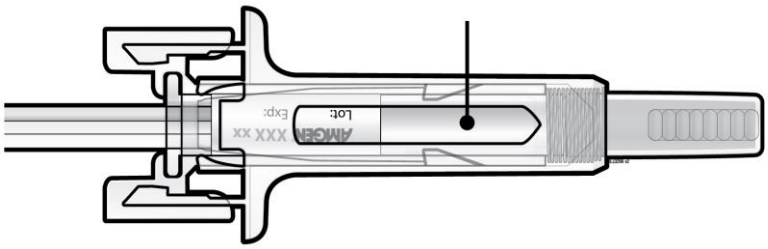
Important
Before you use an Aranesp pre-filled syringe with automatic needle guard, read this important information: • It is important that you do not try to give yourself the injection unless you have received training from your doctor or healthcare provider. • Aranesp is given as an injection into 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 and may cause severe allergic reactions. ✘ **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. ✘ **Do not** attempt to remove the peelable label on the pre-filled syringe barrel before administering your injection. 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).
Put the original package with any unused pre-filled syringes back in the refrigerator. 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.

Medicine

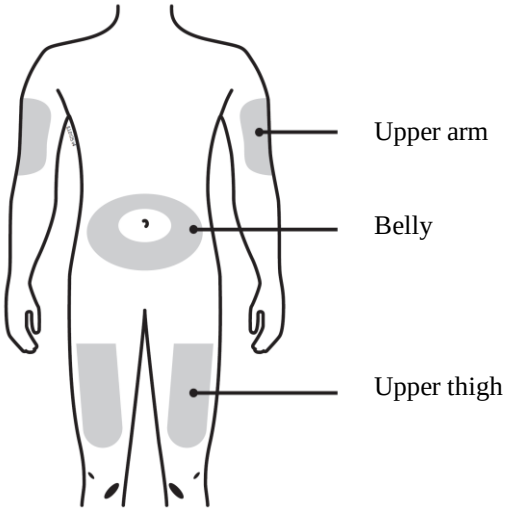


✘ **Do not** use the pre-filled syringe if:

- The medicine is cloudy or there are particles in it. It must be a clear and colorless liquid.
- 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 your hands thoroughly. Prepare and clean your injection site.



You can use:

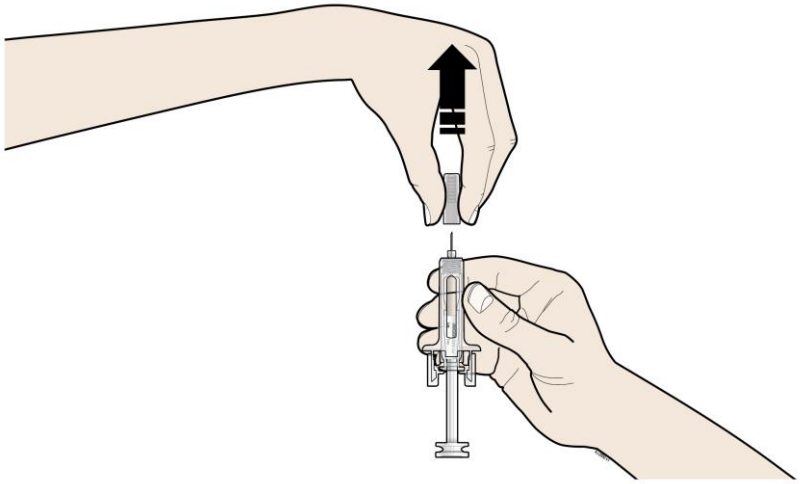
- Upper part of your thigh
- Belly, except for a 5 cm (2-inch) area right around your belly button
- Outer area of upper arm (only if someone else is giving you the injection)

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

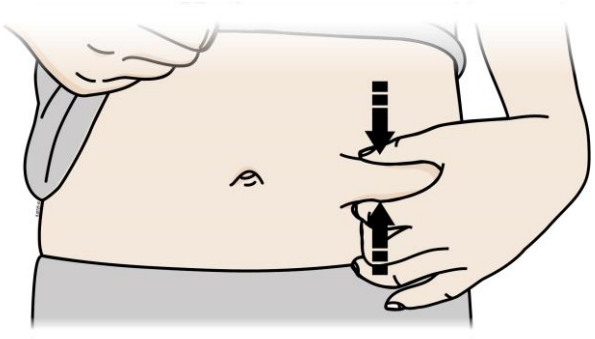
✘ **Do not** touch the injection site before injecting

Choose a different site each time you give yourself an injection. If you need to use the same injection site, just make sure it is not the same spot on that site you used last time.
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 grey needle cap straight out and away from your body.

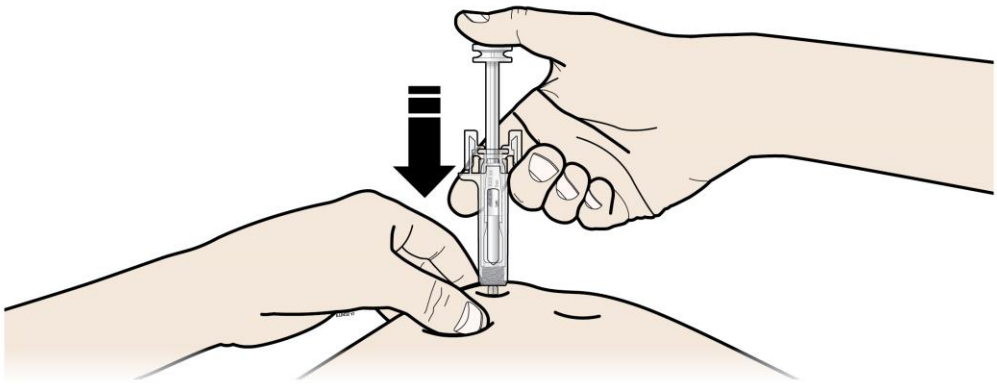


C	Pinch your injection site to create a firm surface.



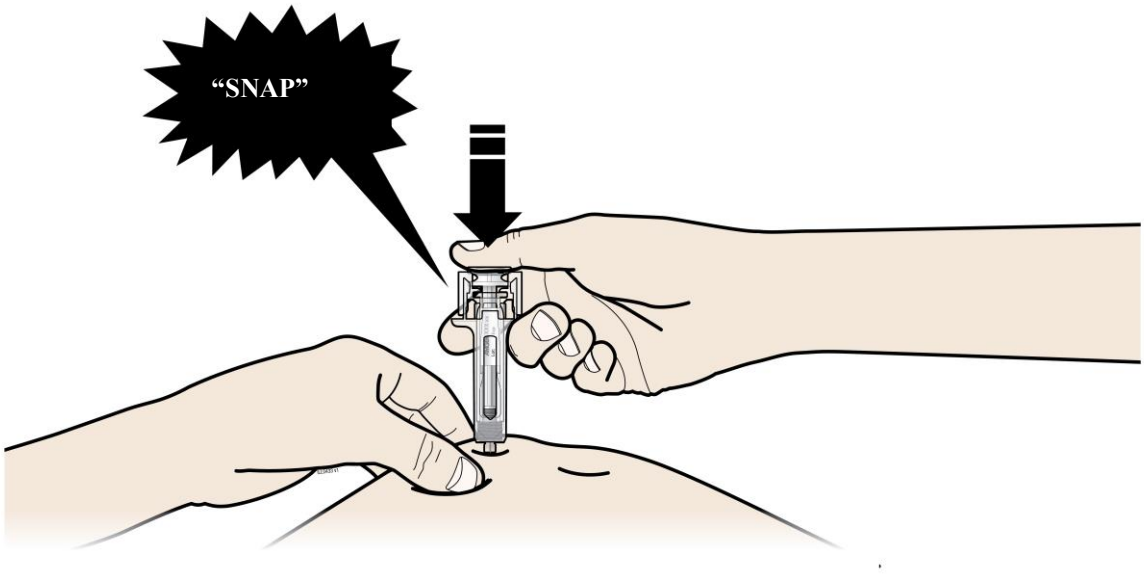
It is important to keep the skin pinched when injecting.

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



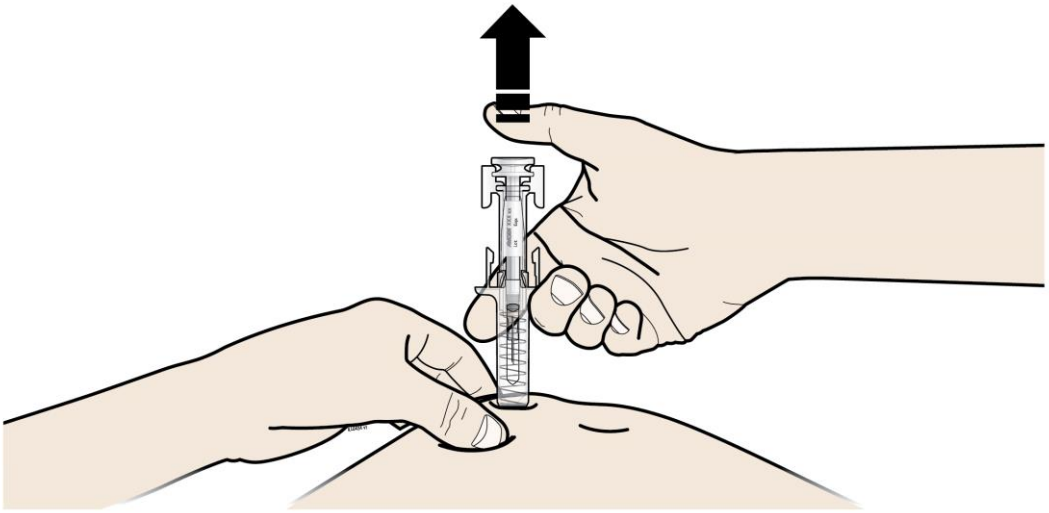
✘ **Do not** touch the cleaned area of the skin.

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



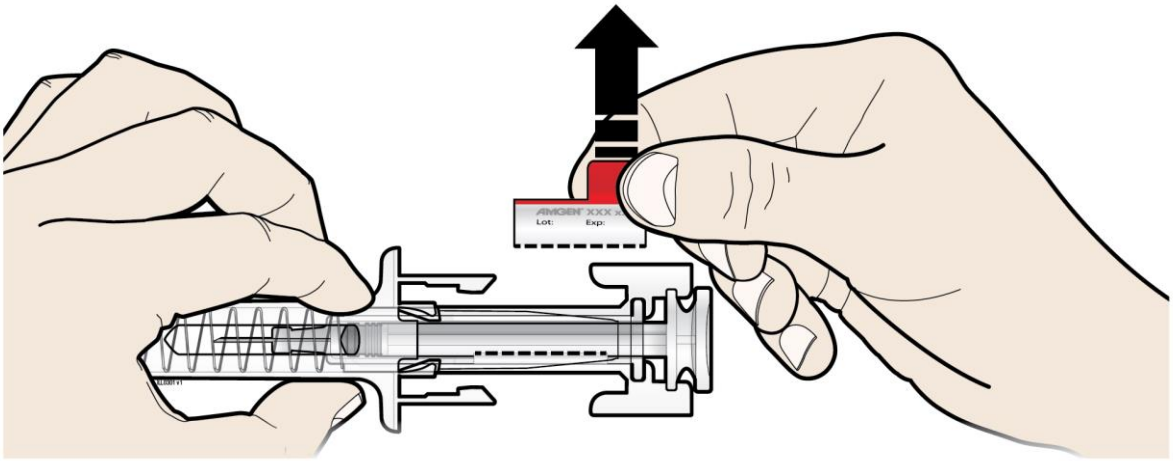
It is important to push down through the “snap” to deliver your full dose.

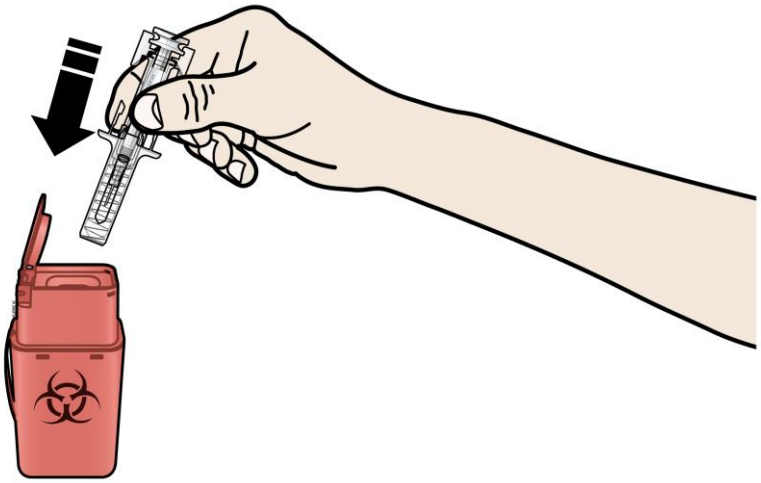
C	RELEASE your thumb. Then LIFT the syringe off skin.



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

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

Healthcare Providers only
Remove and save the pre-filled syringe label.  Turn the plunger to move the label into a position where you can remove the syringe label.

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.	