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 pen (SureClick®) 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 pen of Aranesp 20 mcg, contains 20 mcg of darbepoetin alfa in 0.5 mL (40 mcg/1 mL)
Each pre-filled pen of Aranesp 30 mcg, contains 30 mcg of darbepoetin alfa in 0.3 mL (100 mcg/1 mL)
Each pre-filled pen of Aranesp 40 mcg, contains 40 mcg of darbepoetin alfa in 0.4 mL (100 mcg/1 mL)
Each pre-filled pen of Aranesp 50 mcg, contains 50 mcg of darbepoetin alfa in 0.5 mL (100 mcg/1 mL)
Each pre-filled pen of Aranesp 60 mcg, contains 60 mcg of darbepoetin alfa in 0.3 mL (200 mcg/1 mL)
Each pre-filled pen of Aranesp 80 mcg, contains 80 mcg of darbepoetin alfa in 0.4 mL (200 mcg/1 mL)
Each pre-filled pen of Aranesp 100 mcg, contains 100 mcg of darbepoetin alfa in 0.5 mL (200 mcg/1 mL)
Each pre-filled pen of Aranesp 150 mcg, contains 150 mcg of darbepoetin alfa in 0.3 mL (500 mcg/1 mL)
Each pre-filled pen of Aranesp 300 mcg, contains 300 mcg of darbepoetin alfa in 0.6 mL (500 mcg/1 mL)
Each pre-filled pen 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 pen 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, under your skin (by subcutaneous injection).

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. Aranesp SureClick® must be injected subcutaneously. 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 pen 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 SureClick®. Do not try to self inject unless you have received an instruction. **Never inject Aranesp into a vein yourself! The pre-filled pen is designed to inject the area under your skin only.**

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 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 pen 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 SureClick® is packed as 1 ready to use pre-filled pen.

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 the MoHs guidelines.

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

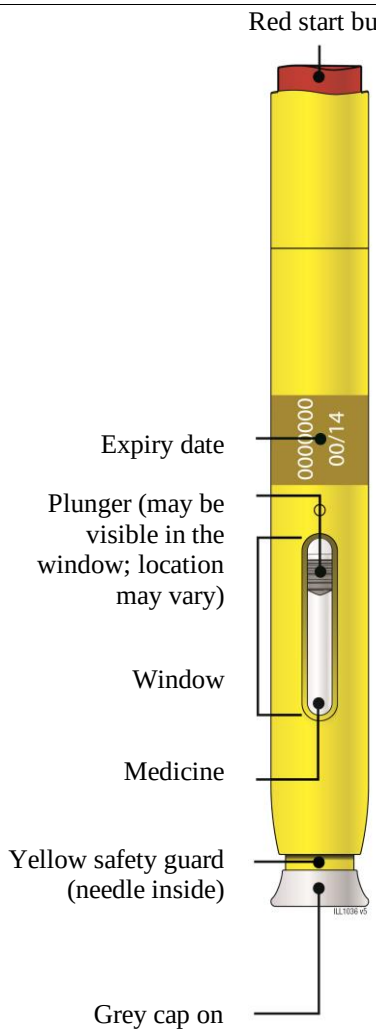
Aranesp 10 mcg: 124 38 30392
Aranesp 20 mcg: 124 40 30394
Aranesp 30 mcg: 124 41 30395
Aranesp 40 mcg: 124 42 30396
Aranesp 50 mcg: 124 43 30397
Aranesp 60 mcg: 124 44 30398
Aranesp 80 mcg: 124 45 30399
Aranesp 100 mcg: 124 46 30400
Aranesp 150 mcg: 124 47 30401
Aranesp 300 mcg: 129 65 30888
Aranesp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

Instructions for use

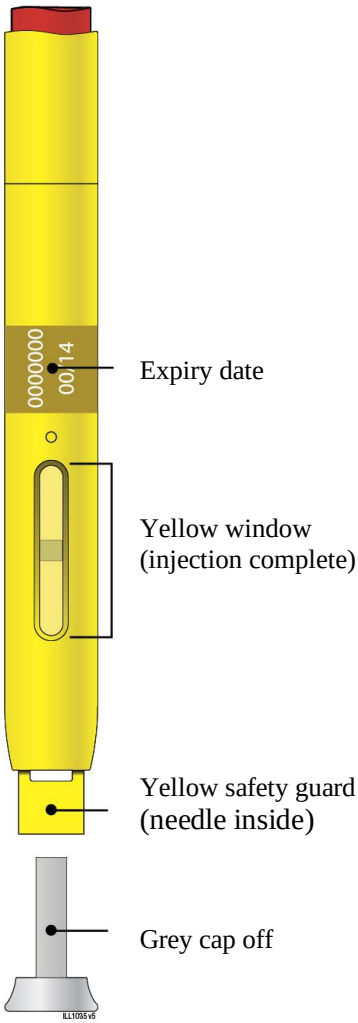
It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider.

Guide to parts

Before use



After use



Important: Needle is inside the yellow safety guard.

Important

Before you use the Aranesp SureClick® pre-filled pen, read this important information:

Storing your Aranesp SureClick® pre-filled pens

- Keep the pre-filled pen and all medicines out of the sight and reach of children.
- Keep the pre-filled pen in the outer carton in order to protect from light or physical damage.
- Store the pre-filled pen in the refrigerator (2°C – 8°C).
- Once your pre-filled pen has been removed from the refrigerator, and left at room temperature (up to 25°C) for approximately 30 minutes before injection, it must either be used within seven days or disposed of.

✘ **Do not** store the pre-filled pen in extreme heat or cold. For example, avoid storing in your car glove box or boot.

✘ **Do not** freeze. Do not use Aranesp if you think it has been frozen.

Using your Aranesp SureClick® pre-filled pens

- Your healthcare provider has prescribed the Aranesp pre-filled pen for injection into the tissue just under the skin (subcutaneous use).

✘ **Do not** use the pre-filled pen after the expiry date on the label. The expiry date refers to the last day of that month.

✘ **Do not** shake the pre-filled pen.

✘ **Do not** remove the grey cap from the pre-filled pen until you are ready to inject.

✘ **Do not** use the pre-filled pen if it has been dropped on a hard surface. Part of the pre-filled pen may be broken even if you cannot see the break. Use a new pre-filled pen.

- The grey cap on the pen contains dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.

For more information or help, contact your healthcare provider.

Step 1: Prepare

A	Remove one pre-filled pen from the carton.

Carefully lift the pre-filled pen straight up out of the carton.
Put the original carton with any unused pre-filled pens back in the refrigerator.
Leave the pre-filled pen at room temperature for at least 30 minutes before injecting.

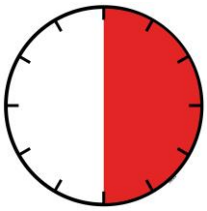
✘ **Do not** put the pre-filled pen back in the refrigerator once it has reached room temperature.

✘ **Do not** try to warm the pre-filled pen by using a heat source such as hot water or microwave.

✘ **Do not** leave the pre-filled pen in direct sunlight.

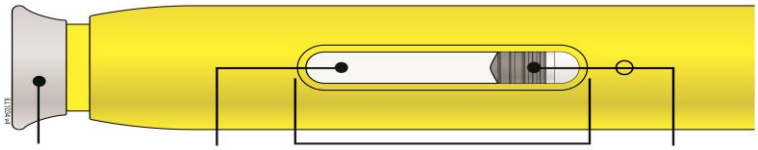
✘ **Do not** shake the pre-filled pen.

✘ **Do not** remove the grey cap from the pre-filled pen yet.



30 minutes

B	Inspect the pre-filled pen.



Grey cap on (needle inside) | Medicine | Window | Plunger (location may vary)

Make sure the medicine in the window is a clear and colorless liquid.

- Check that it is the correct dose that your healthcare provider has prescribed.
- **You may see the plunger in the inspection window at a different location, depending upon the strength.**

✘ **Do not** use the pre-filled pen if the medicine is cloudy or discolored or contains flakes or particles.
✘ **Do not** use the pre-filled pen if any part appears cracked or broken.
✘ **Do not** use the pre-filled pen if the grey cap is missing or not securely attached.
✘ **Do not** use the pre-filled pen if the expiry date printed after EXP on the label has passed.

In all cases, use a new pre-filled pen and contact your healthcare provider.

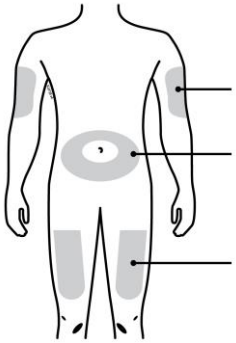
C	Gather all the materials needed for your injection.

Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the:

- New pre-filled pen
- Alcohol wipes
- Cotton ball or gauze pad
- Plaster
- Sharps disposal container

D	Prepare and clean your injection site.



Upper arm

Stomach area (abdomen)

Thigh

You can use:

- Your thigh.
- Your stomach area (abdomen), except for a **5 cm (2-inch)** area right around your navel.
- The 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 this area again before injecting.

- Choose a different site each time you give yourself an injection. If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.

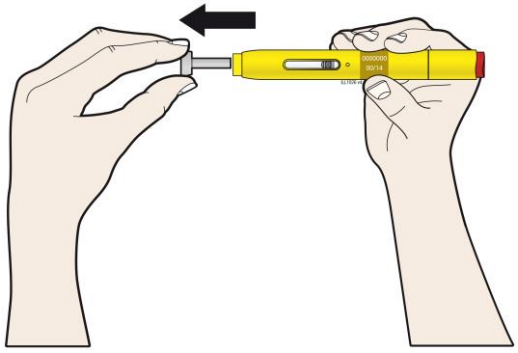
✘ **Do not** inject into areas where the skin is tender, bruised, red, or hard.

- Avoid injecting into raised, thick, red, or scaly skin patches or lesions, or areas with scars or stretch marks.

Important: Follow your healthcare provider's instructions about selecting sites for injection appropriate to you and about changing the site for each injection.

Step 2: Get ready

E	Pull the grey cap straight off, only when you are ready to inject. **Do not** leave the grey cap off for more than five minutes. This can dry out the medicine.



It is normal to see a drop of liquid at the end of the needle or yellow safety guard.

✘ **Do not** twist or bend the grey cap.

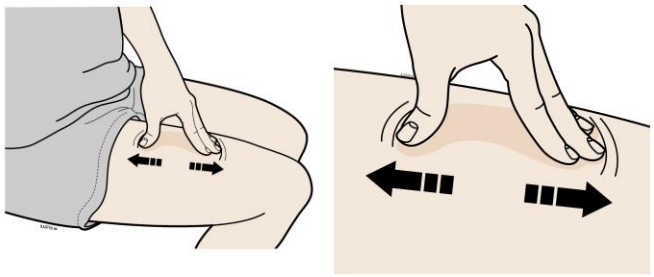
✘ **Do not** put the grey cap back onto the pre-filled pen.

✘ **Do not** remove the grey cap from the pre-filled pen until you are ready to inject.

If you are unable to inject, please contact your healthcare provider immediately.

F	Stretch or pinch your injection site to create a firm surface.

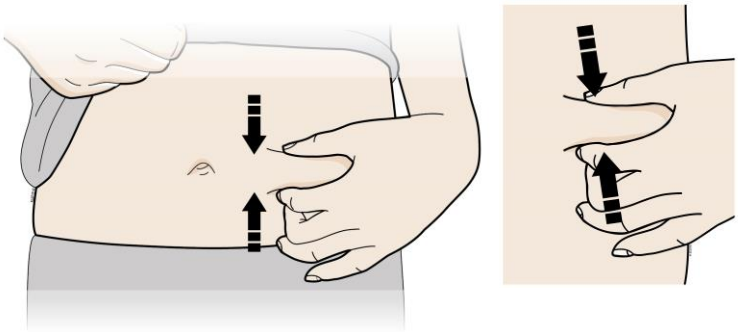
Stretch method



Stretch your skin firmly by moving your thumb and fingers in opposite directions, creating an area about **5 cm (2-inches)** wide.

OR

Pinch method

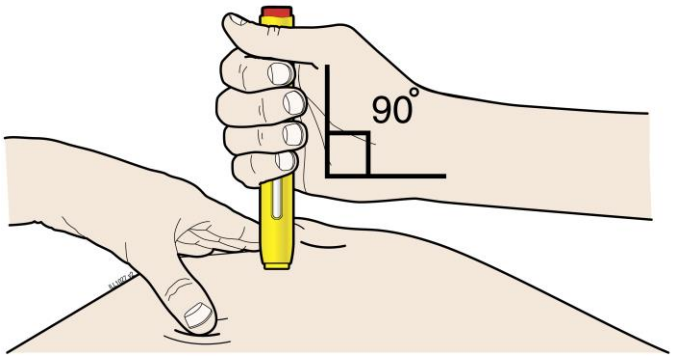


Pinch your skin firmly between your thumb and fingers, creating an area about **5 cm (2-inches)** wide.

Important: It is important to keep your skin stretched or pinched while injecting.

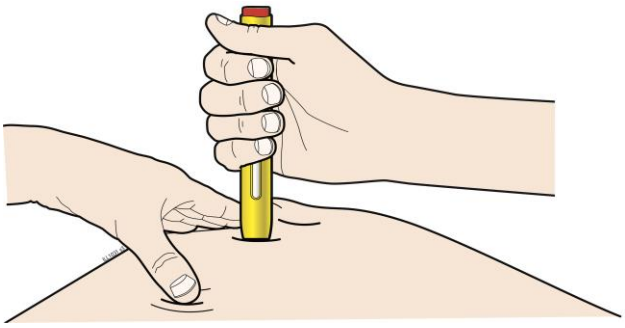
Step 3: Inject

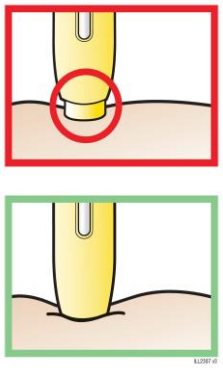
G	Keep stretching or pinching your skin. With the grey cap off, **place** the pre-filled pen on your skin at 90 degrees.



Important: Do not touch the red start button yet.

H	Firmly **push** the pre-filled pen down onto your skin until it stops moving. The safety guard retracts when pushed onto a firm injection site.

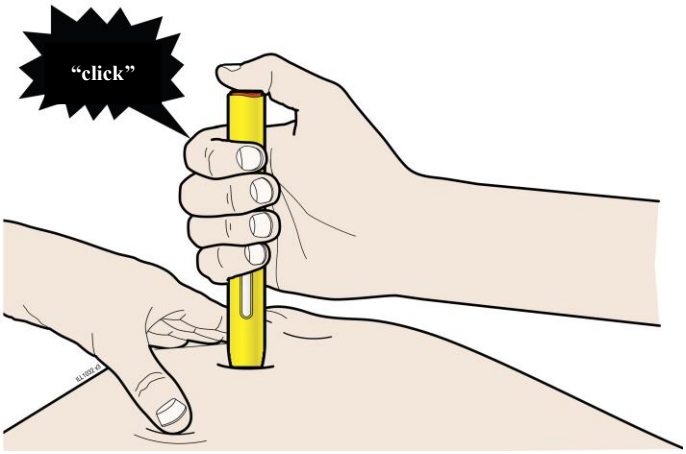




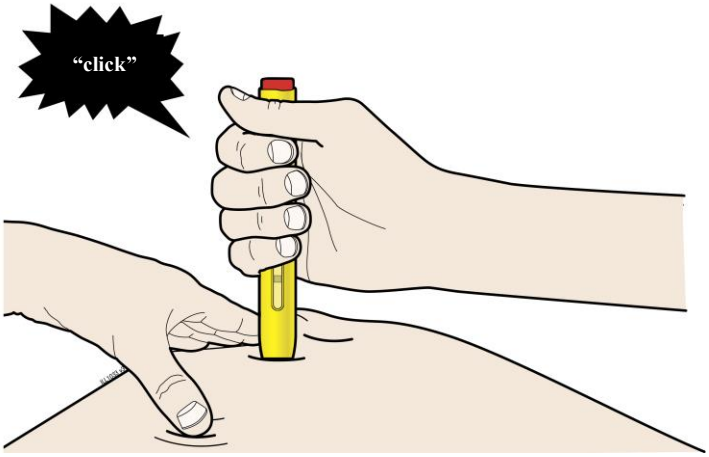
Yellow safety guard retracted.

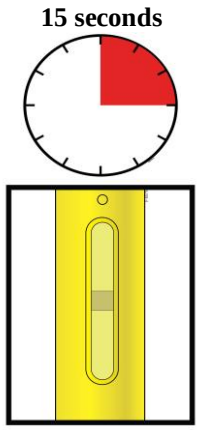
Important: You must push the pre-filled pen all the way down but do not touch the red start button until you are ready to inject.

I	When you are ready to inject, **press** the red start button.

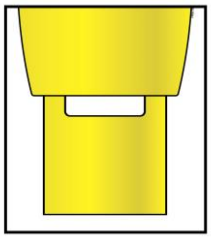


J	Keep **pushing** the pre-filled pen down on your skin. Your injection could take about **15** seconds.





Window turns yellow when the injection is done



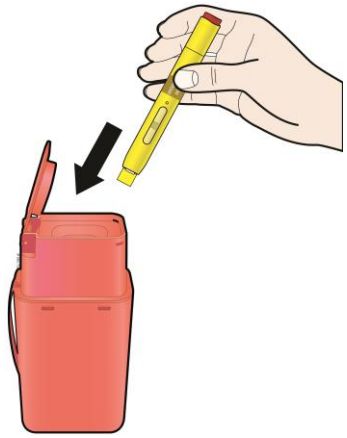
Note: After you remove the pre-filled pen from your skin, the needle will be automatically covered.

Important: When you remove the pre-filled pen, if the window has not turned yellow, or if it looks like the medicine is still injecting, this means you have not received a full dose. Contact your healthcare provider immediately.

K	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.

Step 4: Finish	
L	Dispose of the used pre-filled pen and grey cap.



Put the used pre-filled pen in the sharps disposal container immediately after use.

- **Do not** reuse the pre-filled pen.
- **Do not** recycle the pre-filled pen or sharps disposal container or throw them into household rubbish.

Talk with your healthcare provider about proper disposal. There may be local guidelines for disposal.

Important: Always keep the sharps disposal container out of the sight and reach of children.