Package leaflet: Information for the user

Benepali 50 mg solution for injection in pre-filled pen
etanercept

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Card, which contains important safety information that you need to be aware of before and during treatment with Benepali.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Benepali is and what it is used for
2. What you need to know before you use Benepali
3. How to use Benepali
4. Possible side effects
5. How to store Benepali
6. Contents of the pack and other information
7. Instructions for use (see overleaf)

1. What Benepali is and what it is used for

Benepali contains the active substance etanercept.

Benepali is a medicine that is made from two human proteins. It blocks the activity of another protein in the body that causes inflammation. Benepali works by reducing the inflammation associated with certain diseases.

In adults (aged 18 and over), Benepali can be used for:
- moderate or severe **rheumatoid arthritis**;
- **psoriatic arthritis**;
- severe **axial spondyloarthritis** including **ankylosing spondylitis**;
- moderate or severe **plaque psoriasis.**

In each case Benepali is used, usually when other widely used treatments have not worked well enough or are not suitable for you.

For **rheumatoid arthritis**, Benepali is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, Benepali can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For **psoriatic arthritis** patients with multiple joint involvement, Benepali can improve your ability to do normal daily activities.

For patients with **multiple symmetrical painful or swollen joints** (e.g., hands, wrists and feet), Benepali can slow down the structural damage to those joints caused by the disease.

Benepali is also prescribed for the treatment of the following diseases in children and adolescents.

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
    - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years and weighing 62.5 kg or more.
    - Psoriatic arthritis in patients from the age of 12 years and weighing 62.5 kg or more.
- For enthesitis-related arthritis in patients from the age of 12 years and weighing 62.5 kg or more when other widely used treatments have not worked well enough or are not suitable for them.
- Severe plaque psoriasis in patients from the age of 6 years and weighing 62.5 kg or more who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

2. What you need to know before you use Benepali

Do not use Benepali

- if you or the child you are caring for, are **allergic to etanercept** or any of the other **ingredients of this medicine** (listed in section 6). If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Benepali, and contact your doctor immediately.
- if you or the child have, or are at risk of developing a **serious blood infection** called sepsis. If you are not sure, please contact your doctor.
- if you or the child have an **infection of any kind**. If you are not sure, please talk to your doctor.

Warnings and precautions

Talk to your doctor before taking Benepali.

- **Allergic reactions:** If you or the child experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more Benepali, and contact your doctor immediately.
- **Infections/surgery:** If you or the child develop a new infection, or are about to have any major surgery, your doctor may wish to monitor the treatment with Benepali.
- **Infections/diabetes:** Tell your doctor if you or the child have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you or the child develop symptoms of an infection such as fever, chills or cough, notify your doctor immediately. Your doctor may decide to continue to monitor you or the child for the presence of infections after you or the child stop using Benepali.
- **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with Benepali, your doctor will check for signs and symptoms of tuberculosis before starting Benepali. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- **Hepatitis B:** Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with Benepali. Treatment with Benepali may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using Benepali.

- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with Benepali in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of Benepali.
- **Nervous system and eye disorders:** Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if Benepali is an appropriate treatment.
- **Congestive heart failure:** Tell your doctor if you or the child have a history of congestive heart failure, because Benepali needs to be used with caution under these circumstances.
- **Cancer:** Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Benepali. Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma. Children and adults taking Benepali may have an increased risk of developing lymphoma or another cancer. Some children and teenage patients who have received etanercept or other medicines that work the same way as etanercept have developed cancers, including unusual types, which sometimes resulted in death. Some patients receiving Benepali have developed skin cancers. Tell your doctor if you or the child develop any change in the appearance of the skin or growths on the skin.
- **Chickenpox:** Tell your doctor if you or the child are exposed to chickenpox when using Benepali. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Alcohol abuse**: Benepali should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- **Wegener's granulomatosis:** Benepali is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- **Anti-diabetic medicines:** Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking Benepali.

Children and adolescents
Benepali is not indicated for use in children and adolescents who weigh less than 62.5 kg.

- **Vaccinations:** If possible, children should be up to date with all vaccinations before using Benepali. Some vaccines, such as oral polio vaccine, should not be given while using Benepali. Please consult your doctor before you or the child receive any vaccines.

Benepali should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 2 years or weighing less than 62.5 kg, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years or weighing less than 62.5 kg, or in children with psoriasis below the age of 6 years or weighing less than 62.5 kg.

Other medicines and Benepali
Tell your doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should **not use** Benepali with medicines that contain the active substance anakinra or abatacept.

Pregnancy and breast-feeding
Benepali should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received Benepali during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received etanercept in pregnancy, compared with mothers who had not received etanercept or other similar medicines (TNF-

antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received etanercept in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby.

Talk to your doctor if you want to breastfeed while on Benepali treatment. It is important that you tell your baby's doctors and other healthcare professionals about the use of Benepali during pregnancy and breastfeeding before your baby receives any vaccine.

Driving and using machines
The use of Benepali is not expected to affect the ability to drive or use machines.

Benepali contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 50 mg, that is to say essentially 'sodium-free'.

3. How to use Benepali

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

If you feel that the effect of Benepali is too strong or too weak, talk to your doctor or pharmacist.

Dosing for adult patients (aged 18 years or over)
Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis
The usual dose is 50 mg once a week as an injection under the skin.
However, your doctor may determine an alternative frequency at which to inject Benepali.

Plaque psoriasis
The usual dose is 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 50 mg once a week.

Your doctor will decide how long you should use Benepali and whether retreatment is needed based on your response. If Benepali has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

Use in children and adolescents
The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of etanercept. Paediatric patients weighing 62.5 kg or more can be dosed 25 mg given twice a week or 50 mg given once a week using a fixed-dose pre-filled syringe or pre-filled pen.

Other etanercept products with appropriate dosage forms for children are available.

For polyarthritis or extended oligoarthritis in patients from the age of 2 years and weighing 62.5 kg or more, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years and weighing 62.5 kg or more, the usual dose is 25 mg given twice a week or 50 mg given once a week.

For psoriasis in patients from the age of 6 years and weighing 62.5 kg or more, the usual dose is 50 mg and should be given once weekly. If Benepali has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

Method and route of administration
Benepali is administered by an injection under the skin (subcutaneous injection).
Benepali can be taken with or without food or drink.

Detailed instructions on how to inject Benepali are provided in section 7 "Instructions for use".
Do not mix the Benepali solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week Benepali should be used.

If you use more Benepali than you should
If you have used more Benepali than you should (either by injecting too much on a single occasion or by using it too frequently), **talk to a doctor or pharmacist immediately**. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Benepali
If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

If you stop using Benepali
Your symptoms may return upon discontinuation.

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

4. Possible side effects

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

Allergic reactions
If any of the following happen, do not inject more Benepali**. Tell your doctor immediately, or go to the casualty department at your nearest hospital.**

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to Benepali, so you should seek immediate medical attention.

Serious side effects
If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints;
- Signs of **blood disorders**, such as bleeding, bruising, or paleness;
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg;
- Signs of **heart failure** or **worsening heart failure**, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips;
- Signs of **cancers:** Cancers may affect any part of the body including the skin and blood, and

possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin;
- Signs of **autoimmune reactions** (where antibodies are made that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision;
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue;
- Signs of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

Other side effects
The known side effects of Benepali include the following in groups of decreasing frequency:

- **Very common** (may affect more than 1 in 10 people)
  Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections); injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) (these do not occur as often after the first month of treatment; some patients have developed a reaction at an injection site that was recently used); and headache.

- **Common** (may affect up to 1 in 10 people)
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).

- **Uncommon** (may affect up to 1 in 100 people)
  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common); abdominal cramps and pain, diarrhoea, weight loss or blood in the stool (signs of bowel problems).

- **Rare** (may affect up to 1 in 1,000 people)
  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon); lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes), opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered), erythema multiforme (inflammatory skin rash), cutaneous vasculitis (inflammation of blood vessels in the skin); damage to nerves, including

Guillain-Barré syndrome (a serious condition which can affect breathing and damage body organs).

- **Very rare** (may affect up to 1 in 10,000 people)
  Failure of the bone marrow to produce crucial blood cells; toxic epidermal necrolysis (a life-threatening skin condition).

- **Not known** (frequency cannot be estimated from available data)
  Merkel cell carcinoma (a type of skin cancer); Kaposi's sarcoma (a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); damage to the tiny filters inside your kidneys leading to poor kidney function (glomerulonephritis); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash); listeria (a bacterial infection).

Additional side effects in children and adolescents
The side effects and their frequencies seen in children and adolescents are similar to those described above.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Benepali

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

Do not use this medicine after the expiry date which is stated on the carton and the label of the pre-filled pen after EXP. 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 pens in the outer carton in order to protect from light.

After taking a pre-filled pen from the refrigerator, **wait approximately 30 minutes to allow the Benepali solution in the pen to reach room temperature**. Do not warm in any other way. Immediate use is then recommended.

Benepali may be stored outside of the refrigerator at temperatures up to a maximum of 30°C for a single period of up to 31 days; after which, it should not be refrigerated again. Benepali should be discarded if not used within 31 days after removal from the refrigerator. It is recommended that you record the date that Benepali is removed from the refrigerator and the date after which Benepali should be discarded (no more than 31 days following the removal from the refrigerator).

Inspect the solution in the pen by looking through the clear inspection window. The solution should be clear to slightly opalescent, colourless or pale yellow, and may contain small white or almost transparent particles of protein. This appearance is normal for Benepali. Do not use this medicine if you notice the solution is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

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 protect the environment.

6. Contents of the pack and other information

What Benepali contains
- The active substance is etanercept. Each pre-filled pen contains 0.98 ml of solution, providing 50 mg of etanercept.
- The other ingredients are sucrose, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate heptahydrate, and water for injections (see section 2 “Benepali contains sodium”).

What Benepali looks like and contents of the pack
Benepali is supplied as a solution for injection in a pre-filled pen (solution for injection). The pen contains a clear to slightly opalescent, colourless or pale yellow solution for injection (injection).

Benepali is available in packs containing 4 pre-filled pens and multipacks comprising 3 cartons, each containing 4 pre-filled pens. Not all pack sizes may be marketed.

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7. Instructions for use

Read the instructions for use before you start using Benepali and each time you get a refill of your prescription. There may be new information.

- **Do not** try to give yourself the injection unless your doctor or nurse has shown you how to give the injection.

A single-use pre-filled pen contains one 50 mg dose of Benepali.

Find a well-lit, clean surface and gather all the equipment you need:

- **A new Benepali pre-filled pen**

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

Not included in pack:

- **1 alcohol swab, gauze pad and plaster**

- **Sharps disposal container**

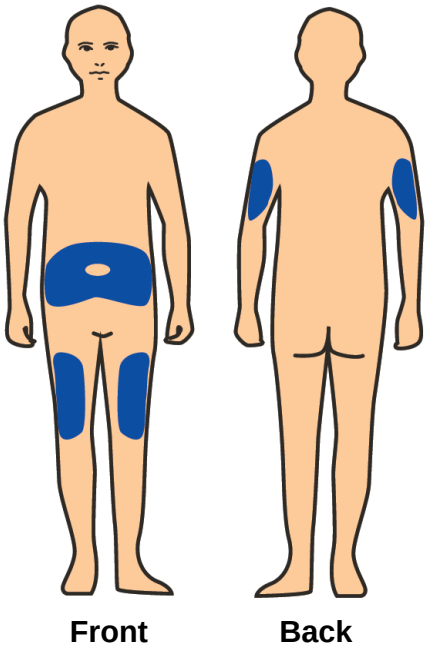
A. Before you start

1. **Inspect the pre-filled pen:**
   Check the expiry date on the pre-filled pen label.
   - **Do not** use the pre-filled pen past the expiration date.
   - **Do not** use the pre-filled pen if it has been dropped onto a hard surface. Components inside the pre-filled pen may be broken.
   - **Do not** use the pre-filled pen if the needle cap is missing or not securely attached.

2. **Inspect the solution:**
   Look at the medicine through the viewing window.
   The medicine should be clear to slightly opalescent, colourless or pale yellow, and may contain small white or almost transparent particles of protein.
   - **Do not** use the solution if it is discoloured, cloudy, or if particles other than those described above are present.

3. **Allow the medicine to reach room temperature:**
   Remove one pre-filled pen from the carton that is stored in the refrigerator and leave at room temperature for at least 30 minutes before injecting.
   This is important to make the medicine easier and more comfortable to inject.
   - **Do not** remove the needle cap until you are ready to inject.
   - **Do not** use heat sources, such as a microwave or hot water, to warm Benepali.

4. Choose an injection site:

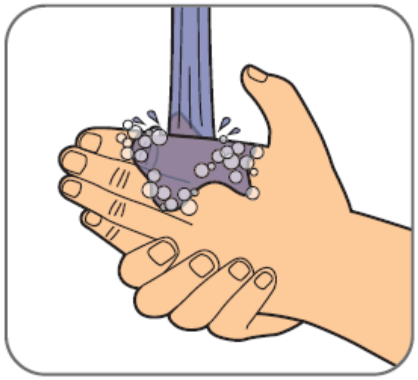


The Benepali pre-filled pen is for a subcutaneous injection. It should be injected into the thigh, abdomen, or back of the upper arm (see image on the left).
Rotate the site for each injection.
If you are injecting into the abdomen, choose a site that is at least 5 cm away from the belly button.

- **Do not** inject into areas that are red, hard, bruised, or tender.
- **Do not** inject into scars or stretch marks.
- If you have psoriasis, **do not** inject into any raised, thick, red, or scaly skin patches, or lesions.

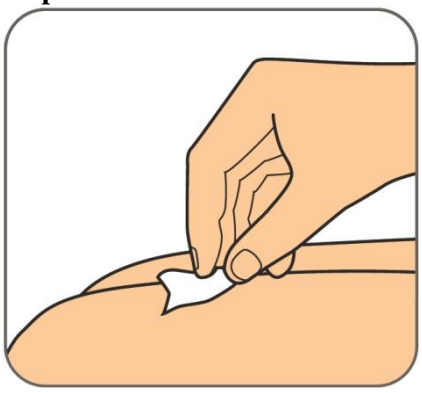
B. Injection steps

Step 1:



Wash your hands with soap and water.

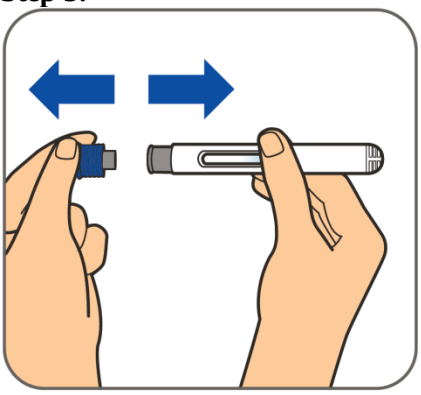
Step 2:



Wipe the skin at the injection site with an alcohol swab.
See 'Choose an injection site' for guidance with choosing an injection site.

- **Do not** touch this area again before giving the injection.

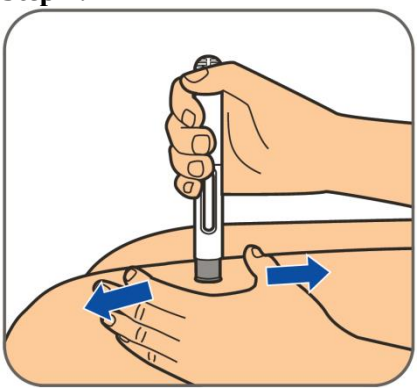
Step 3:



Pull the needle cap straight off and dispose of it in the bin or sharps container.

- **Do not** twist or bend the needle cap while removing it, as this may damage the needle. Do not recap the needle.
- **Never recap the needle.**

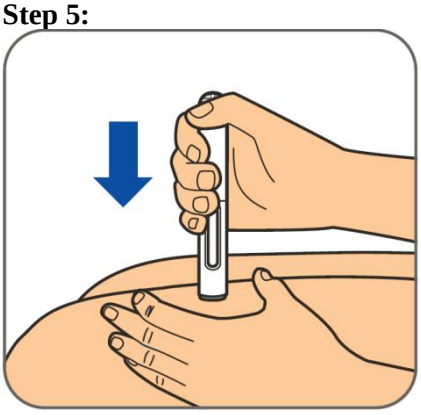
Step 4:



Gently stretch the skin at the cleaned injection site.
Position the pre-filled pen approximately 90 degrees to the skin.

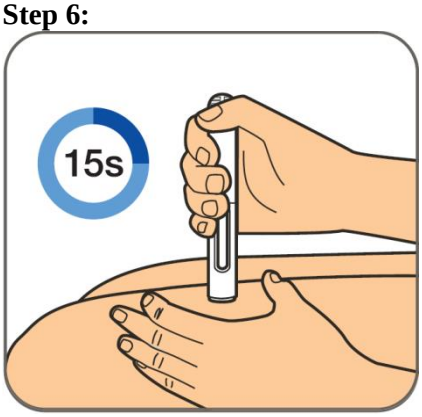
- **Do not** pinch the skin.
- Stretching the skin creates a firm surface.

Step 5:



Firmly press the pre-filled pen down into the site to start the injection.
The device will click when the injection begins.
Continue to hold the pre-filled pen firmly pressed into the site.
The device will click a second time.

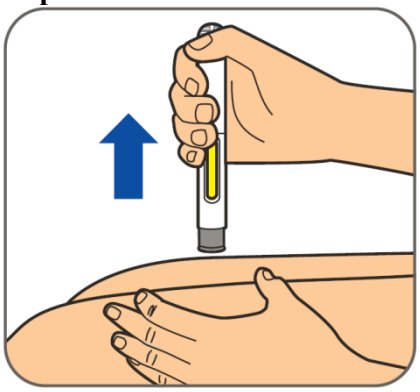
Step 6:



After the second click, count slowly to 15 to make sure that the injection is complete.

- **Do not** release pressure against the injection site before the injection is complete.
- **Do not** move the pre-filled pen during the injection.

Step 7:



Remove the empty pen from the skin.
The needle guard will completely cover the needle.
Check for the yellow plunger rod in the window to confirm that the full dose has been delivered.

Disposal:

Dispose of the empty pen in an approved sharps container.
Check with your healthcare provider for instructions on how to properly dispose a filled sharps container. Sharps disposal containers may be purchased at your local pharmacy.

- **Do not** throw the sharps container in household bin.
- **Do not** recycle.
- **Always keep the container out of the sight and reach of children.**

C. Injection site care

If there is bleeding at the injection site, press a gauze pad over the injection site.

- **Do not** rub the injection site.

If needed, cover the injection site with a plaster.