

PATIENT PACKAGE INFORMATION ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

This medicine is dispensed with a doctor's prescription only

HADLIMA

Solution for Injection

Each pre-filled syringe/pre-filled pen contains: Adalimumab 40 mg

Inactive ingredients and allergens: See section 6 'Further Information' and in section 2 'Important information regarding some of the ingredients of the medicine.'

Read this leaflet carefully in its entirety before using the medicine.

This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat your ailment. 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 leaflet, there is a "Patient safety information card" for the preparation Hadlima solution for injection. This card contains important safety information, that you should know before starting treatment and during the treatment with Hadlima solution for injection and act accordingly. Refer to the "Patient safety information card" and the patient leaflet before you start using this preparation. The card should be kept for further review if necessary.

For your attention, it is important that each time you receive the medicine at the pharmacy, make sure that you receive the same medicine that your expert doctor prescribed for you. If the medicine you receive appears different from the one you normally receive or the instructions of use have changed, please contact the pharmacist immediately to make sure you have received the correct medicine. Any replacement or dosage change of a medicine containing adalimumab must be made only by the expert attending doctor. Please check that the brand name of the preparation prescribed by your expert doctor is identical to the name of the medicine that you received from the pharmacist.

1. WHAT IS THE MEDICINE INTENDED FOR?

Hadlima is intended for the treatment of:

- moderate to severe, active rheumatoid arthritis in adults, when other accepted treatment has been inadequate.
- severe, active and progressive rheumatoid arthritis in adults, not previously treated with methotrexate.
- severe active ankylosing spondylitis in adults, when other accepted treatment has been inadequate.
- severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults, when there was an inadequate response to, or intolerance to non-steroidal anti-inflammatory drugs (NSAIDs).
- active and progressive psoriatic arthritis in adults, when other accepted treatment has been inadequate.
- moderate to severe plaque psoriasis in adults, who are candidates for systemic therapy.
- active, moderate to severe hidradenitis suppurativa in adults, when accepted treatment has been inadequate.
- moderate to severe, active Crohn's disease in adults, when other accepted treatment has either been inadequate or is inappropriate.
- active, moderate to severe ulcerative colitis in adults, when other accepted treatment has been inadequate, or in patients who can't receive other accepted treatments.
- uveitis – inflammation of the uvea (panuveitis, posterior or intermediate), from a non-infectious source, in adults, when treatment with steroids is inappropriate or inadequate.
- intestinal Behçet's disease in adults, when other accepted treatment has been inadequate.

Therapeutic group: immunosuppressant, Tumour Necrosis factor alpha (TNF- α) inhibitor.

Hadlima contains the active substance adalimumab, a medicine that acts on your body's immune (defence) system.

The target of adalimumab is a protein called tumour necrosis factor (TNF α), which is present at increased levels in the inflammatory diseases listed above. By attaching to TNF α , Hadlima decreases the process of inflammation in these diseases.

2. BEFORE USING THE MEDICINE

Do not use this medicine if:

- you are sensitive (allergic) to adalimumab or to any of the other ingredients contained in this medicine. For the list of inactive ingredients, see section 6 'Further Information'.
- you have a severe infection, including tuberculosis (see "Special warnings regarding use of the medicine"). It is important that you tell your doctor if you have symptoms of infections, e.g. fever, wounds, feeling tired, dental problems.
- you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Special warnings regarding use of the medicine").

Special warnings regarding use of the medicine

Before taking the medicine, tell your doctor if:

Allergic reaction

If you have **allergic reactions** with symptoms such as chest tightness, wheezing, dizziness, swelling or rash, do not inject more Hadlima and contact your doctor immediately, since in rare cases, these reactions can be life-threatening.

Infection

If you have an **infection**, including long-term or localised infection (for example, leg ulcer), consult your doctor before starting Hadlima. If you are unsure, contact your doctor.
You might get infections more easily while you are receiving Hadlima treatment. This risk may increase if your lung function is impaired. These infections may be serious and include tuberculosis, infections caused by viruses, fungi, parasites or bacteria, other opportunistic infections (unusual infections associated with a weakened immune system) and sepsis (blood poisoning). In rare cases, these infections may be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend temporary discontinuation of Hadlima.

Tuberculosis

As cases of **tuberculosis** have been reported in patients treated with Hadlima, your doctor will check you for signs and symptoms of tuberculosis before starting treatment with Hadlima. This will include a thorough medical evaluation, including your medical history and screening tests (for example chest X-ray and a tuberculin test). The tests and their results should be documented on your Patient Card. It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. Tuberculosis can develop during therapy even if you have received preventative treatment for tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.

Travel/recurrent infections

Tell your doctor if you reside or travel in regions where fungal infections such as histoplasmosis, coccidioidomycosis or blastomycosis are endemic.
Tell your doctor if you have a history of recurrent infections or other conditions that increase the risk of infections.

Hepatitis B Virus

Tell your doctor if you are a carrier of the **Hepatitis B Virus (HBV)**, if you have active HBV infection or if you think you might be at risk of contracting HBV. Your doctor should test you for HBV. Hadlima can reactivate HBV infection in people who carry this virus. In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV infection can be life-threatening.

Age over 65 years

If you are **over 65 years**, you may be more susceptible to infections while taking Hadlima. You and your doctor should pay special attention for signs of infection while you are being treated with Hadlima. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

Surgery or dental procedure

If you are about to have **surgery or dental procedures** tell your doctor that you are taking Hadlima. Your doctor may recommend temporary discontinuation of Hadlima.

Demyelinating disease

If you have or develop **demyelinating disease** (a disease that affects the insulating layer around the nerves, such as multiple sclerosis), your doctor will decide if you should receive or continue to receive Hadlima. Tell your doctor immediately if you get symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

Vaccines

Certain **vaccines** contain weakened but live forms of disease-causing bacteria or viruses, and these vaccines should not be given while receiving Hadlima. Check with your doctor before you receive any vaccines. If you receive Hadlima while you are pregnant, your baby may be at higher risk for getting an infection for up to about five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals that you used Hadlima during your pregnancy so that they can decide when your baby should receive any vaccine.

Heart failure

If you have **mild heart failure** and you are being treated with Hadlima, you should be closely monitored for your heart failure condition by your doctor. It is important to tell your doctor if you have had or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Hadlima.

Fever, bruising, bleeding or pallor

In some patients the body may fail to produce enough of the blood cells to fight off infections or help you to stop bleeding. If you develop a **fever** that does not go away, or you **bruise** or **bleed** very easily or look very **pale**, call your doctor right away. Your doctor may decide to stop treatment.

Cancer

There have been very rare cases of certain kinds of **cancer** in children and adults taking Hadlima or other TNF- α blockers. People with more serious rheumatoid arthritis who have had the disease for a long time may have a higher than average risk of getting **lymphoma** (a cancer that affects the lymph system), and leukaemia (a cancer that affects the blood and bone marrow). If you take Hadlima the risk of getting lymphoma, leukaemia, or other cancers may increase. In rare cases, a specific and severe type of lymphoma has been observed in patients taking Hadlima. Some of those patients were also treated with the medicines azathioprine or mercaptopurine. Tell your doctor if you are taking azathioprine or mercaptopurine with Hadlima.
In addition, cases of **non-melanoma skin cancer** have been observed in patients taking Hadlima. If new areas of damaged skin appear during or after therapy or if existing marks or areas of damage change appearance, tell your doctor.
There have been cases of **cancers, other than lymphoma** in patients with a specific type of lung disease called chronic obstructive pulmonary disease (COPD) treated with another TNF- α blocker. If you have COPD, or you are a heavy smoker, you should discuss with your doctor whether treatment with a TNF α blocker is appropriate for you.

Lupus-like syndrome

On rare occasions, treatment with Hadlima could result in lupus-like syndrome. Contact your doctor if symptoms such as persistent unexplained rash, fever, joint pain or tiredness occur.

Smoking

If you are a heavy smoker, you should discuss with your doctor whether treatment with a TNF- α blocker is appropriate for you (see above in section "Special warnings regarding use of the medicine").

Children and adolescents

Hadlima is not indicated for use in children and adolescents under 18 years of age.

Drug interactions

If you are taking, have recently taken or if you might take, other medicines, including **non-prescription medicines and nutritional supplements, tell the doctor or pharmacist**. Especially if you are taking:

Hadlima can be taken together with methotrexate or certain disease-modifying anti-rheumatic agents (sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations), corticosteroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

Do not take Hadlima with medicines containing the following active substances for the treatment of rheumatoid arthritis, due to increased risk of serious infection:

- anakinra
- abatacept

If you have questions, please ask your doctor.

Pregnancy and breast-feeding

You should consider using appropriate contraception to prevent pregnancy and continue its use for at least 5 months after the last injection of Hadlima.
If you are pregnant, think if you may be planning to have a baby, ask your doctor for advice about taking this medicine.
Hadlima should only be used during a pregnancy, if needed.
According to a study done in pregnancy, there was no higher risk of birth defects when the mother received adalimumab during pregnancy compared with mothers with the same disease who did not receive adalimumab.
Hadlima can be used during breast-feeding.

If you received Hadlima during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your use of Hadlima during pregnancy, before the baby receives any vaccine (for more information on vaccines see in section "Special warnings regarding use of the medicine").

Driving and use of machines

Hadlima may have a minor influence on your ability to drive, ride a bicycle or use machines. After taking Hadlima there may be a feeling that the room is spinning (vertigo) and vision disturbances.

Important information regarding some of the ingredients of the medicine

Hadlima contains sodium and sorbitol:

This medicinal product contains 20 mg sorbitol in each pre-filled syringe/ pre-filled pen. If you have been told by your doctor that you have an intolerance to certain sugars, contact your doctor before taking this medicinal product.

Also, this medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, which means it is essentially sodium-free.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use this preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and method of treatment.
The dosage and method of treatment will be determined by the doctor only.

Do not exceed the recommended dose.

Method and route of administration

Hadlima is given by injection under the skin (subcutaneous injection). For instructions for use, refer to section 7 'Instructions for use'.

If you accidentally took a higher dosage

If you accidentally inject Hadlima more frequently than you should, call your doctor or pharmacist and explain that you have taken a higher dosage. Always take the outer carton of the medicine with you, even if it is empty.
If a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine at the required time, do not take a double dose. Remember, then, take your next dose as you would have taken it on your originally scheduled day, had you not forgotten a dose.

If you stop using Hadlima

The decision to stop using Hadlima should be discussed with your doctor. Your symptoms may return upon stopping treatment.

Adhere to the treatment as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Hadlima may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur up to 4 months or more after the last injection of Hadlima.

Stop taking the medicine and seek medical advice immediately, if you notice the following side effects:

- severe rash, hives or other signs of allergic reaction;
- swollen face, hands, feet;
- trouble breathing, swallowing;
- shortness of breath with exertion or upon lying down or swelling of the feet.

Tell your doctor as soon as possible if you notice any of the following side effects:

- signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
 - feeling weak or tired;
 - coughing;
 - tingling;
 - numbness;
 - double vision;
 - weakness in the arm or leg;
 - a bump or open sore that doesn't heal;
 - signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, pallor.
- The symptoms described above can be signs of the below listed side effects, which have been observed with adalimumab:

Very common side effects (may affect more than 1 in 10 people):

- injection site reactions (including pain, swelling, redness or itching);
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia);
- headache;
- abdominal (belly) pain;
- nausea and vomiting;
- rash;
- pain in the muscles.

Common side effects (may affect up to 1 in 10 people):

- serious infections (including blood poisoning and influenza);
- intestinal infections (including gastroenteritis);
- skin infections (including cellulitis and shingles);
- ear infections;
- mouth infections (including tooth infections and cold sores);
- reproductive tract infections;
- urinary tract infection;
- fungal infections;
- joint infections;
- benign tumours;
- skin cancer;
- allergic reactions (including seasonal allergy);
- dehydration;
- mood swings (including depression);
- anxiety;
- difficulty sleeping;
- sensation disorders such as tingling, prickling or numbness;
- migraine;
- symptoms of nerve root compression (including low back pain and leg pain);
- vision disturbances;
- eye inflammation;
- inflammation of the eyelid and eye swelling;
- vertigo (sensation of the room spinning);
- sensation that the heart is beating rapidly;
- high blood pressure;
- flushing;
- haematoma (a solid swelling with clotted blood);
- cough;
- asthma;
- shortness of breath;
- gastrointestinal bleeding;
- dyspepsia (indigestion, bloating, heart burn);
- acid reflux disease;
- sicca syndrome (including dry eyes and dry mouth);
- itching;
- itchy rash;
- bruising;
- inflammation of the skin (such as eczema);
- breaking of finger nails and toe nails;
- increased sweating;
- hair loss;
- new onset or worsening of psoriasis;
- muscle spasms;
- blood in urine;
- kidney problems;
- chest pain;
- oedema (a build up of fluid in the body which causes the affected tissue to swell);
- fever;
- reduction in blood platelets which increases risk of bleeding or bruising;
- impaired healing.

Uncommon side effects (may affect up to 1 in 100 people):

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered);
- neurological infections (including viral meningitis);
- eye infections;
- bacterial infections;
- diverticulitis (inflammation and infection of the large intestine);
- cancer, including cancer of the lymph system (lymphoma) and melanoma (a type of skin cancer);
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly as a condition called sarcoidosis);
- vasculitis (inflammation of blood vessels);
- tremor;
- neuropathy (nerve damage);
- stroke;
- hearing loss, buzzing;
- feeling of irregular heartbeats such as missing beats;
- heart problems that can cause shortness of breath or ankle swelling;
- myocardial infarction;
- a sac formation in the wall of a major artery, inflammation and clot in a vein; blockage of a blood vessel;
- lung diseases causing shortness of breath (including inflammation);
- pulmonary embolism (blockage in the artery of the lung);
- pleural effusion (abnormal collection of fluid in the pleural space);
- inflammation of the pancreas which causes severe pain in the abdomen and back;
- difficulty in swallowing;
- facial oedema;
- gallbladder inflammation, gallbladder stones;
- fatty liver (build up of fat in liver cells);
- night sweats;
- scarring;
- abnormal muscle breakdown;
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems);
- sleep interruptions;
- impotence;
- inflammations.

Rare side effects (may affect up to 1 in 1,000 people):

- leukaemia (cancer affecting the blood and bone marrow);
 - severe allergic reaction with shock;
 - multiple sclerosis;
 - nerve disorders (such as inflammation of the optic nerve in the eye, and Guillain-Barré syndrome, a condition that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body);
 - heart stops pumping;
 - pulmonary fibrosis (scarring of the lung);
 - intestinal perforation;
 - hepatitis;
 - reactivation of hepatitis B;
 - autoimmune hepatitis (inflammation of the liver caused by the body's own immune system);
 - cutaneous vasculitis (inflammation of blood vessels in the skin);
 - Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash);
 - facial oedema associated with allergic reactions;
 - erythema multiforme (inflammatory skin rash);
 - lupus like syndrome;
 - angioedema (localized swelling of the skin);
 - Icthenoid skin reaction (itchy reddish-purple skin rash).
- Side effects of unknown frequency** (frequency cannot be estimated from available data):
- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
 - 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.
 - liver failure;
 - worsening of a condition called dermatomyositis (inflammation of skin and muscles, seen as a skin rash accompanying muscle weakness).

Some side effects observed with adalimumab may not have symptoms and may only be discovered through blood tests. These include:

Very common side effects (may affect more than 1 in 10 people):

- low blood measurements for white blood cells;
- low blood measurements for red blood cells;
- increased lipids in the blood;
- raised liver enzymes.

Common side effects (may affect up to 1 in 10 people):

- high levels of white blood cells;
- low platelets levels in the blood;
- increased uric acid in the blood;
- abnormal blood measurements for sodium;
- low levels of calcium in the blood;
- low levels of phosphate in the blood;
- high blood sugar;
- high levels of lactate dehydrogenase in the blood;
- autoantibodies present in the blood;
- low levels of potassium in the blood.

Uncommon side effects (may affect up to 1 in 100 people):

- high levels of bilirubin (blood test for liver function).

Rare side effects (may affect up to 1 in 1,000 people):

- low levels of white blood cells, red blood cells and platelets.

If a side effect occurs, if any of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult the doctor.

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 SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine, and all other medicines, must be stored in a safe place out of the reach and sight of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- **Pre-filled syringe/ pre-filled pen**
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled syringe/ pre-filled pen in the outer carton in order to protect from light.
Alternative Storage:
A single Hadlima pre-filled syringe/ pre-filled pen may be stored at temperatures up to maximum of 25°C for a period of up to 28 days. The syringe or pen must be protected from light and discarded if not used within the 28-day period.
You should record the date on which the syringe/pen was first removed from refrigerator, and the date after which it should be discarded.
- 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. FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains: Sorbitol, L-histidine hydrochloride monohydrate, Sodium citrate dihydrate, L-histidine, Polysorbate 20, Citric acid monohydrate, Water for injection.
- What does the medicine look like and what are the contents of the package?
Hadlima solution for injection in a pre-filled syringe or in a pre-filled pen is dispensed as a clear to opalescent, colourless to pale brown solution of 0.8 ml.
Hadlima is available in packs containing 2 pre-filled syringes or 2 pre-filled pens.
- **Registration Holder and address:**
Samsung Bioepis L. Ltd., Alboa Hill 14, Ramat-Gan

• **Manufacturer and address:**
Biogen (Denmark) Manufacturing AP, Hillerød, Denmark

• Approved in February 2021

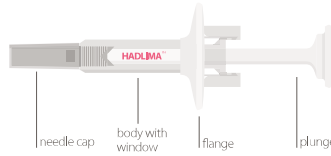
• **Registration number of the medicine in the National Drug Registry of the Ministry of Health:**
16676-36272-00

7. INSTRUCTIONS FOR USE

Follow this instruction guide carefully, and soon you will develop a routine for injecting confidently.

- Before you inject, ask your doctor or nurse to show you how to use your pre-filled syringe. Your doctor or nurse should make sure you can use your syringe correctly.

Your single-dose pre-filled syringe



After you push the plunger all the way down, the needle will retract to help prevent needle stick injury.

Caring for your pre-filled syringe

- Syringe storage**
- Store your syringe in the refrigerator, but do not freeze it.
 - Keep your syringe in its carton, and away from light.
 - Keep the syringe out of the sight and reach of children.

Syringe disposal

- Use each syringe only once. Never reuse a syringe.
- Throw away your used syringe in a special container as instructed by your doctor, nurse or pharmacist.

Cautions

- If you dropped your syringe with the cap ON, it is okay to use the syringe.
- If you dropped your syringe with the cap OFF, do not use it. The needle might be dirty or damaged.
- Do not use a damaged syringe.

Injection site care

- Choose a fatty area for injection:
Fatty areas, like your stomach, are generally the best injection sites. Fatty areas are easier to pinch and are good for inserting the needle correctly.
- Use a different injection site every time:
When choosing an injection site, select an area that has not recently been used to avoid soreness and bruises.
- Press plunger slowly:
Sometimes, fast injections can be painful. If you press the syringe plunger slowly, it may make your injection more comfortable.

How to inject with your pre-filled syringe

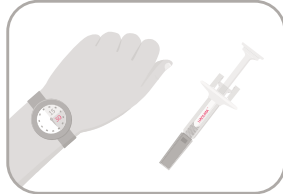
1. Gather supplies



Place your pre-filled syringe and alcohol pads on a clean, dry surface.

- Remember to wash your hands!
- Do not remove the cap just yet!

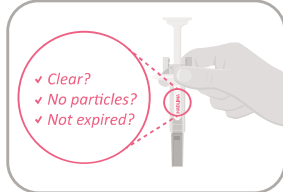
2. Wait 15-30 minutes



Wait 15–30 minutes for your pre-filled syringe to reach to room temperature, which helps reduce your pain during injection.

- Do not remove the cap just yet!

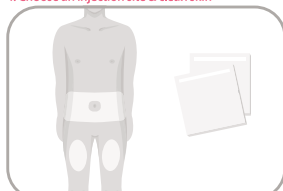
3. Inspect medicine & expiration date



Always make sure your medicine is clear, free of particles, and has not expired. If your medication is not clear, free of particles, or expired, do not use it.

- You may see 1 or more bubbles, and that is okay. There is no reason to remove it.
- Do not remove the cap just yet!

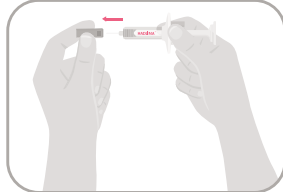
4. Choose an injection site & clean skin



Choose an injection site on your body. Your abdomen (except the area around the navel) or thighs are best. Clean your injection site with an alcohol pad. Do not touch the area again before the injection.

- Avoid skin that is sore, bruised, scarred, scaly, or has red patches.

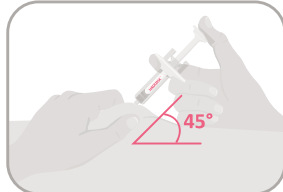
5. Pull off needle cap



Carefully pull off the needle cap.

It is normal to see a few drops of liquid come out of the needle. If you take off the needle cap before you are ready to inject, **do not put the needle cap back on**. This could bend or damage the needle. You might accidentally stick yourself or waste medication.

6. Pinch skin & insert needle



Gently pinch your skin and insert the needle all the way at about a 45-degree angle.

####