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

This medicine is dispensed with a doctor's prescription only

StimoFil 300 mcg/0.5 ml
Solution for infusion or injection

Active ingredient and concentration:
Each 0.5 ml contains:
filgrastim 300 micrograms

StimoFil 480 mcg/0.5 ml
Solution for infusion or injection

Active ingredient and concentration:
Each 0.5 ml contains:
filgrastim 480 micrograms

Inactive ingredients and allergens in the product - see section 2 under 'Important information about some of this medicine's ingredients', and section 6 'Additional information'.

Read the entire leaflet carefully before you start using this medicine.
This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor, nurse or pharmacist.
This medicine has been prescribed to treat your medical condition. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

Please note that every time you get this medicine at the pharmacy, it is important that you check that you have been given the same medicine that your specialist has prescribed you. If the medicine you are given looks different from what you usually get, or if the instructions for use have changed, please consult your pharmacist immediately to make sure you received the correct medicine. Only your specialist can switch your medicine or change the dosage of medicine that contains filgrastim. Please check that the medicine that your specialist prescribed you has the same brand name as the medicine you got from the pharmacist.

1. What is this medicine intended for?

StimoFil can be used:
- to increase the number of white blood cells after treatment with chemotherapy to help prevent infections.
- to increase the number of white blood cells after a bone marrow transplant to help prevent infections.
- before high-dose chemotherapy to make the bone marrow produce more stem cells which can be collected and given back to you after your treatment. These can be taken from you or from a donor. The stem cells will then go back into the bone marrow and produce blood cells.
- to increase the number of white blood cells if you suffer from severe chronic neutropenia (SCN), to help prevent infections.
- in patients with advanced HIV infection will which help reduce the risk of infections.

Therapeutic group: cytokines

StimoFil is a white blood cell growth factor (granulocyte-colony stimulating factor) and belongs to a group of medicines called cytokines. Growth factors are proteins that are produced naturally in the body, but they can also be made using biotechnology for use as a medicine.
StimoFil works by encouraging the bone marrow to produce more white blood cells.
A reduction in the number of white blood cells (neutropenia) can occur for several reasons and makes your body less able to fight infections.

StimoFil stimulates the bone marrow to produce new white cells quickly.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient filgrastim or to any of the other ingredients in this medicine (see section 6 'Additional information').

Special warnings about using this medicine

Talk to your doctor, pharmacist or nurse before using StimoFil.

- **Before using StimoFil, tell your doctor if:**
  - you have sickle cell anemia, as StimoFil may cause sickle cell crisis.
  - you have osteoporosis (bone disease).
  - you have an allergy to natural rubber (latex). The needle cover on the syringe may be made from a type of natural rubber and may cause allergic reactions.

- **Please tell your doctor immediately during treatment with StimoFil, if:**
  - sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing appear, as these may be signs of a severe allergic reaction (hypersensitivity).
  - you notice puffiness in your face or ankles, blood in your urine or brown-colored urine or you notice you urinate less than usual (glomerulonephritis).
  - you have left upper belly pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of an enlarged spleen [splenomegaly], or possibly rupture of the spleen).
  - you notice unusual bleeding or bruising (these may be symptoms of a decrease in blood platelet count [thrombocytopenia], with a reduced ability of your blood to clot).
  - you have symptoms of inflammation of the aorta (the large blood vessel which transports blood from the heart to the body). This has been reported rarely in cancer patients and healthy donors. The symptoms of the inflammation may include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience these symptoms.

Children and adolescents

StimoFil is used to treat children who are receiving chemotherapy or who suffer from severe low white blood cell count (neutropenia). The dose children receiving chemotherapy is the same as for adults.

Tests and follow-up

If you suffer from severe chronic neutropenia, it is recommended that during treatment with StimoFil, periodic tests be performed to check the bone marrow status.

Loss of response to filgrastim

If you experience a loss of response or failure to maintain a response with filgrastim treatment, your doctor will investigate the reasons why including whether you have developed antibodies which neutralize filgrastim's activity.
Your doctor may want to monitor you closely (see section 4 'Side effects').

If you have severe chronic neutropenia, you may be at risk of developing cancer of the blood [leukemia, myelodysplastic syndrome (MDS)]. You should consult your doctor about your risks of developing cancer of the blood and what follow-up testing should be done. If you develop or are at risk of developing cancer of the blood, you should not use StimoFil, unless your doctor explicitly directs you otherwise.

If you are a stem cell donor, you must be aged between 16 and 60 years.

Take special care with other medicines that stimulate production of white blood cells.
StimoFil is one of a group of medicines that stimulates the production of white blood cells. Your healthcare professional should always document the exact medicine you are using.

Interactions with other medicines
If you are taking or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist.
Do not start treatment with StimoFil from 24 hours before and until 24 hours after receiving chemotherapy.

Pregnancy and breast-feeding
The medicine has not been tested in pregnant or breast-feeding women.
The medicine is not recommended for use during pregnancy.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to become pregnant, it is important that you tell your doctor before taking this medicine.
If you become pregnant during StimoFil treatment, please inform your doctor.
Unless your doctor directs you otherwise, you must stop breast-feeding if you use StimoFil.

Driving and using machines
StimoFil may have a minor influence on your ability to drive and operate machines. This medicine may cause dizziness. It is advisable to wait and see how you feel after taking StimoFil and before driving or operating machinery.

Important information about some of this medicine's ingredients
- This medicine contains sorbitol. Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.
  You must tell your doctor before receiving this medicine if you have HFI or if you can no longer consume sweet foods or drinks because they make you feel sick, vomit or have unpleasant effects such as bloating, stomach cramps or diarrhea.
- This medicine contains less than 1 mmol sodium (23 mg) sodium per dose (pre-filled syringe), that is to say essentially 'sodium-free'.

3. How to use this medicine?
Always use this medicine according to your doctor's instructions. Check with your doctor, nurse or pharmacist if you are not sure about your dose or about how to take this medicine.
Only your doctor will determine your dose and how you should take this medicine.

How is StimoFil given and how much should I take?
StimoFil is usually given as a daily injection into the tissue just under the skin (known as a subcutaneous injection). It can also be given as a daily slow injection into the vein (known as an

intravenous infusion). The usual dose varies depending on your illness and weight. Your doctor will tell you how much StimoFil you should take.

Patients having a bone marrow transplant after chemotherapy:
You will generally receive your first dose of StimoFil at least 24 hours after your chemotherapy and at least 24 hours after receiving your bone marrow transplant.

You, or people caring for you, can learn how to give subcutaneous injections so that you can continue your treatment at home. However, you should not attempt this unless you have been properly trained first by your healthcare provider.
Please read the instructions for self-injection of StimoFil that appear at the end of this leaflet.

Do not exceed the recommended dose.

Treatment duration
You will need to take StimoFil until your white blood cell count is normal. Regular blood tests will be taken to monitor the number of white blood cells in your body. Your doctor will tell you how long you will need to take StimoFil.

If you have accidentally taken a higher dose
Do not increase the dose your doctor has given you. If you think you have injected more than required, contact your doctor as soon as possible.
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take StimoFil
If you have missed an injection, or injected too little, contact your doctor as soon as possible. Do not take a double dose to make up for any missed doses.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor, nurse or pharmacist.

If you stop taking this medicine
Your doctor will tell you when to stop using the medicine. Several treatment cycles with StimoFil may be necessary.

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

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects

As with any medicine, using StimoFil may cause side effects in some users. Do not be alarmed by this list of side effects. You may not experience any of them.

Refer to your doctor immediately if during treatment:

- you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), skin rash, itchy rash (urticaria), swelling of the face, lips, mouth, tongue or throat (angioedema) and shortness of breath (dyspnea).
- you experience a cough, fever and difficulty breathing (dyspnea). They may be a sign of Acute Respiratory Distress Syndrome (ARDS).
- if you experience kidney injury (glomerulonephritis). Kidney injury has been observed in patients who received StimoFil. Contact your doctor if you suffer from puffiness in your face or ankles, blood in your urine or brown-colored urine or you notice you urinate less than usual.
- you have any of the following or combination of the following side effects: swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop rapidly.

These could be symptoms of a condition called capillary leak syndrome which causes blood to leak from the small blood vessels into your body and needs urgent medical care.

- if you have a combination of any of the following symptoms: fever, or shivering, or feeling very cold, fast heart rate, confusion or disorientation, shortness of breath, extreme pain or discomfort and clammy or sweaty skin.

These could be symptoms of a condition called “sepsis” (also called blood poisoning). This is a severe infection with whole-body inflammatory response which can be life-threatening and needs urgent medical care.

- you have left upper belly pain, pain below the left rib cage or at the tip of your left shoulder, as they may be related to a problem with your spleen (enlargement of the spleen [splenomegaly] or rupture of the spleen).
- you are being treated for severe chronic neutropenia, and you have blood in your urine (hematuria). Your doctor may regularly test your urine if you suffer from this side effect or if protein is found in your urine (proteinuria).

<u>Additional side effects</u>

A common side effect of StimoFil use is pain in your muscles or bones (musculoskeletal pain). This can be alleviated by taking standard pain relief medicines.

In patients undergoing a stem cell or bone marrow transplant, Graft versus Host Disease (GvHD) may occur. This is a reaction of the donor cells against the patient receiving the transplant; signs and symptoms include rash on the palms of your hands or soles of your feet and ulcers and sores in your mouth, gut, liver, skin, eyes, lungs, vagina and joints.

Very commonly seen in normal stem cell donors is increase in white blood cells (leukocytosis) and decrease of platelets which reduces the ability of blood to clot (thrombocytopenia), these will be monitored by your doctor.

Very common side effects (occur in more than 1 in 10 patients):

- vomiting
- nausea
- unusual hair loss or thinning (alopecia)
- tiredness (fatigue)
- soreness and swelling of the digestive tract - from the mouth to the anus (mucosal inflammation)

- decrease in platelet count which reduces the ability of blood to clot (thrombocytopenia)
- Decrease in number of red blood cells (anemia)
- fever
- headache
- diarrhea

Common side effects (appear in 1-10 in 100 patients):
- inflammation of the bronchia (bronchitis)
- upper respiratory tract infection
- urinary tract infection
- decreased appetite
- trouble sleeping (insomnia)
- dizziness
- decreased feeling of sensitivity, especially in the skin (hypoesthesia)
- tingling or numbness of the hands or feet (paresthesia)
- low blood pressure (hypotension)
- high blood pressure (hypertension)
- cough
- coughing up blood (hemoptysis)
- pain in your mouth and throat (oropharyngeal pain)
- nose bleeds (epistaxis)
- constipation
- oral pain
- enlargement of the liver (hepatomegaly)
- rash
- redness of the skin
- muscle spasm
- pain when passing urine (dysuria)
- chest pain
- pain
- generalized weakness (asthenia)
- generally feeling unwell (malaise)
- swelling in the hands and feet (edema peripheral)
- increase of certain enzymes in the blood
- changes in blood chemistry
- transfusion reaction

Uncommon side effects (appear in 1-10 in 1,000 patients):
- increase in number of white blood cells (leukocytosis)
- allergic reaction (hypersensitivity)
- rejection of transplanted bone marrow (graft versus host disease)
- high uric acid levels in the blood, which may cause gout. Increased blood uric acid is also called hyperuricemia
- liver damage caused by blocking of the small veins within the liver (veno-occlusive disease)
- lungs do not function as they should, causing breathlessness (respiratory failure)
- swelling and/or fluid in the lungs (pulmonary edema)
- inflammation of the lungs (interstitial lung disease)
- abnormal x-rays of the lungs (lung infiltration)

- bleeding from the lung
- lack of absorption of oxygen in the lung (hypoxia)
- bumpy skin rash (maculo-papular rash)
- disease which causes bones to become less dense, making them weaker, more brittle and increases the risk of fractures (osteoporosis)
- injection site reaction

Rare side effects (appear in 1-10 in 10,000 patients):
- inflammation of aorta (the large blood vessel which transports blood from the heart to the body), (See section 2 'Before using the medicine')
- severe pain in the bones, chest, gut or joints (sickle cell anemia with crisis)
- sudden life-threatening allergic reaction (anaphylactic reaction)
- pain and swelling of the joints, similar to gout (pseudogout)
- a change in how your body regulates the balance of fluids within your body and may result in puffiness (fluid volume disturbances)
- inflammation of the blood vessels in the skin (cutaneous vasculitis)
- plum-colored, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweets syndrome)
- worsening of rheumatoid arthritis
- unusual change in the urine
- bone density decreased

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects
You can report side effects to the Ministry of Health by following the 'Reporting Side Effects of Drug Treatment' link on the Ministry of Health home page (www.health.gov.il), which opens an online form for reporting side effects, or you can also use this link:
https://sideeffects.health.gov.il

5. How to store the medicine?
- **Prevent poisoning!** To prevent poisoning, keep this and all other medicines in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by your doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package and on the label of the pre-filled syringe. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C). Do not freeze.
- The syringe can be removed from the refrigerator and left at room temperature (not above 25°C) for a single period of up to 15 days, or until the expiry date that appears on the package, whichever comes first. At the end of this period, do not put the syringe back into the refrigerator. It must be discarded.
- Store in the original package to protect from light.
- Do not use this medicine if the liquid appears cloudy, discolored, or contains particles. Do not shake.
- Do not throw away medicines via wastewater or household waste. Dispose of the syringe as directed by the doctor, nurse or pharmacist. The needle safety guard prevents needle stick injuries after use.

6. Additional information

In addition to the active ingredient, this medicine also contains:
D-Sorbitol, glacial acetic acid, sodium hydroxide, polysorbate 80, water for injection

What the medicine looks like and contents of the pack:
A clear, colorless solution in a pre-filled syringe marked with 1/40 printed markings from 0.1 ml to 1 ml and an injection needle attached to the syringe.
Each pre-filled syringe contains 0.5 ml of solution.
Each pack contains 1, 3, 5 or 10 pre-filled syringes with a needle safety guard. Each syringe is in a separate blister.
Not all pack sizes may be marketed.

Registration holder's name and address: Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Petah Tikva.

Manufacturer's name and address: Intas Pharmaceuticals Ltd., Gujarat, India.

This leaflet was revised in February 2024 according to Ministry of Health guidelines.

Registration number of the medicine in the Ministry of Health's National Drug Registry:
StimoFil 300 mcg/0.5 ml: 164-19-36445-00
StimoFil 480 mcg/0.5 ml: 164-20-36446-00

Information for self-injection
This section contains information on how to give yourself the injection. Do not try to give yourself an injection of the medicine unless you have received special training from your doctor or nurse. If you are not sure about giving yourself the injection or you have any questions, contact your doctor or nurse for help.

How should you inject yourself with StimoFil?
You will need to inject yourself with the medicine into the tissue under the skin (subcutaneous injection). Give the injection at the same time every day.

Equipment that you need
To give yourself a subcutaneous injection, you will need:
- a pre-filled syringe of StimoFil
- an alcohol wipe or similar means of disinfection

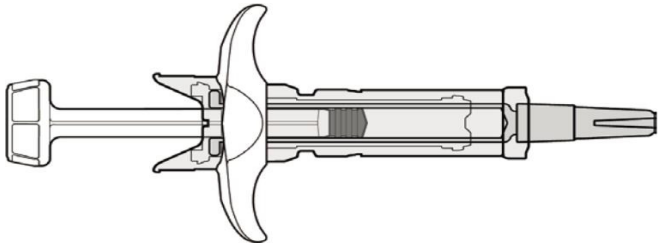
What do you need to do before giving yourself a subcutaneous injection of StimoFil?
Make sure that the needle cover remains on the syringe until you are ready to inject.
A. Remove the pre-filled StimoFil syringe from the refrigerator.
B. Check the expiry date on the pre-filled syringe label (EXP). Do not use the medicine after the expiry date (the expiry date refers to the last day of that month) or if the syringe was stored outside the refrigerator for more than 15 days.
C. Check the appearance of medicine. The liquid in the syringe must be clear and colorless. If there are particles in the liquid, you must not use the medicine.
D. For a more comfortable injection, keep the pre-filled syringe outside of the refrigerator for 30 minutes to reach room temperature or hold the pre-filled syringe gently in your hand for a few minutes. Do not warm the pre-filled syringe in any other way (for example, **do not** warm it in a microwave or in hot water).

E. **Wash your hands thoroughly.**
F. Find a comfortable, well-lit place and put all the equipment you need within reach (the pre-filled syringe and alcohol wipe).

How should you prepare the StimoFil syringe?
Before you inject the medicine, you must do the following:
Do not use the pre-filled syringe if it has been dropped on a hard surface.

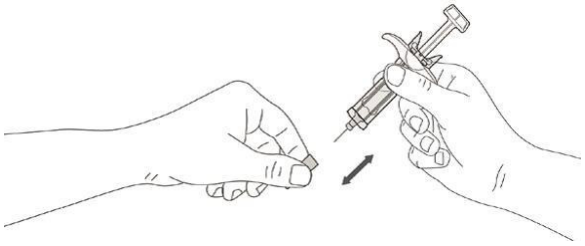
Step 1: Check the integrity of the system
Ensure that the system is intact, not damaged. Do not use the product if you see any damage (syringe or needle safety guard breakage), or if there are any lose components. Ensure that the needle safety guard is not on safety position before use as shown in figure 8, because this indicates that the syringe has already been activated. In general, the medicine should not be used if it does not conform to the diagram presented in figure 1.

Figure 1



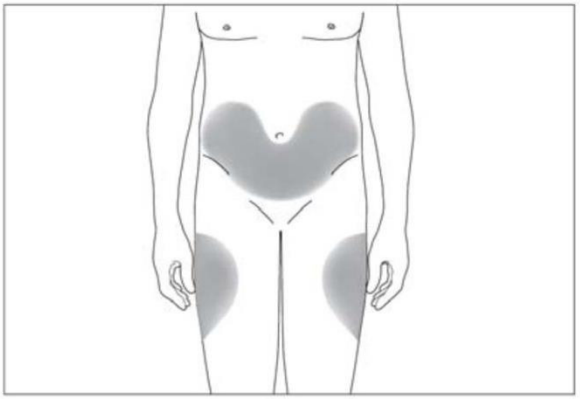
Step 2: Remove the needle cap
1. Remove the needle cap as shown in figure 2. Hold the needle cap in one hand with the needle tip pointing away from you without touching the syringe plunger. Pull the needle cap straight off with your other hand, and discard the needle cap in the waste container.
2. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
3. The syringe may contain more liquid than you need. Use the scale on the syringe as follows to set the correct dose of StimoFil prescribed by your doctor. Eject unnecessary liquid by pushing the plunger up to the number (mL) on the syringe that matches the prescribed dose.
4. Check again to make sure that the correct dose of StimoFil is in the syringe.
5. You can now use the pre-filled syringe.

Figure 2



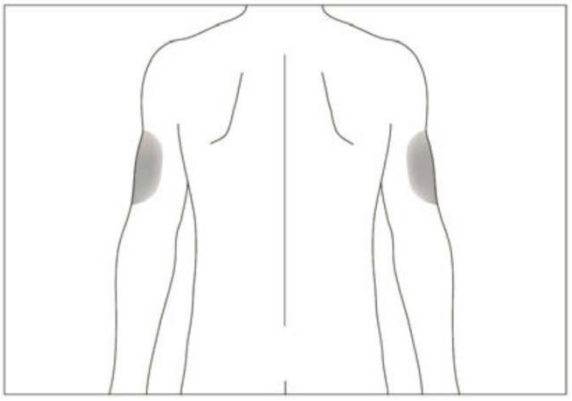
Where should you inject the medicine?
The most suitable places for self-injection are:
- top of the thighs
- the abdomen, except for the areas around the navel (see figure 3).

Figure 3



If someone else is injecting the medicine to you, it is also possible to inject in the back of the arms (see figure 4)

Figure 4



It is recommended to change the injection site every day to avoid the risk of soreness at one site.

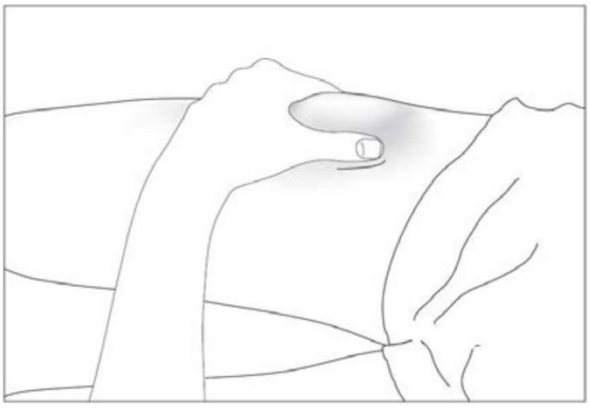
Step 3: Insert the needle

- Lightly pinch the skin at the injection site with one hand.
- With the other hand insert the needle into the injection site (at a 45-90 degree angle) without touching the syringe plunger (see figure 6).

How should you inject the medicine?

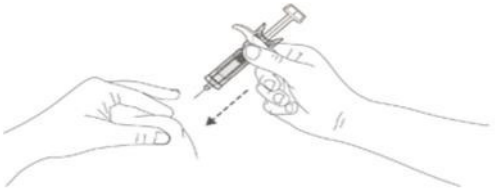
Disinfect the injection site with an alcohol wipe and pinch the skin (without squeezing it) between your thumb and forefinger (see figure 5).

Figure 5



1. Insert the needle fully into the skin as shown by your nurse or doctor (see figure 6).
2. Pull the plunger slightly to check that a blood vessel has not been punctured. If you see blood in the syringe, remove the needle and re-insert it in another place.
3. Inject only the dose prescribed by your doctor according to the instructions below.

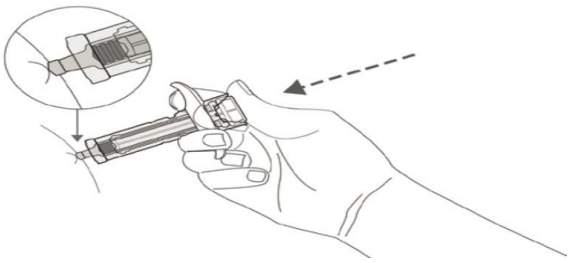
Figure 6



Step 4: Injection

Place the thumb on the plunger head. Push the plunger firmly until the entire dose is injected to ensure emptying of the entire syringe content (see figure 7). Continue holding the skin until the injection is completed.

Figure 7

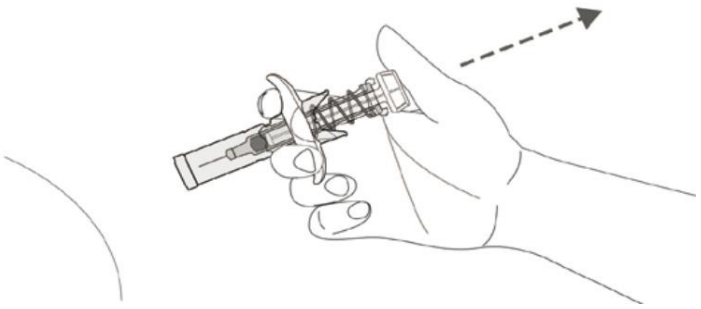


Step 5: Needle stick protection

The safety system will be activated once the plunger is fully depressed.

- Keep the syringe still and slowly lift your thumb from the plunger head.
- The plunger will move up with your thumb, the spring will retract the needle from the injection site into its safety guard (figure 8).

Figure 8



Remember
If you have any problems, do not be afraid to ask your doctor or nurse for help and advice.

Disposing of used syringes
The needle safety guard prevents needle stick injuries after use, so no special precautions for syringe disposal are required. Dispose of the syringe as instructed by your doctor, nurse or pharmacist.