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

This medicine is dispensed with a doctor's prescription only

TEVAGRASTIM® 30 MIU/0.5 ml
Solution for injection or infusion
Pre-filled syringe with needle safety guard

TEVAGRASTIM® 48 MIU/0.8 ml
Solution for injection or infusion
Pre-filled syringe with needle safety guard

Composition:
Filgrastim 30 million IU (300 micrograms) in 0.5 ml

Filgrastim 48 million IU (480 micrograms) in 0.8 ml

For information about inactive ingredients and allergens see section 2 '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 or pharmacist.
This medicine has been prescribed to treat your illness. 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 to confirm 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 a medicine that contains filgrastim (the active ingredient in this medicine). 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?

Treating decreased white blood cell count (neutropenia) caused by chemotherapy, after bone marrow transplantation, in patients with severe chronic neutropenia, in AIDS (HIV) patients, and for mobilization of stem cells to the peripheral blood in case of cell transplantation.

Filgrastim is a white blood cell growth factor (granulocyte colony stimulating factor) and belongs to a group of proteins 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. Filgrastim works by encouraging the bone marrow to produce more white blood cells.

Therapeutic group:
White blood cell (granulocyte) growth factor.

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 2 'Important information about some of this medicine's ingredients' and section 6 'Additional information').

Special warnings about using this medicine
Before using Tevagrastim, tell your doctor if you have:
- sickle cell anemia, as this medicine may cause sickle cell crisis
- osteoporosis (bone disease)

Talk to your doctor immediately during treatment with Tevagrastim, if:
- You have 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 as these could be signs of a severe allergic reaction (hypersensitivity).
- You experience puffiness in your face or ankles, blood in your urine or brown-colored urine or you notice you urinate less than usual (glomerulonephritis).
- You get left upper abdominal pain or pain at the tip of your shoulder (these may be symptoms of an enlarged spleen or possibly rupture of the spleen).
- You notice unusual bleeding or bruising (these may be symptoms of a decrease in blood platelets (thrombocytopenia), with a reduced ability of your blood to clot).
- Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms may include fever, abdominal pain, feeling generally unwell, back pain, and increased inflammatory markers. Tell your doctor if you experience these symptoms.

Children and adolescents
Tevagrastim is used to treat children who are receiving chemotherapy or who suffer from severe low white blood cell count (neutropenia). The dosing in children receiving chemotherapy is the same as for adults.

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 of the package leaflet.

If you are a patient with severe chronic neutropenia, you may be at risk of developing cancer of the blood (leukemia, myelodysplastic syndrome [MDS]). You should talk to your doctor about your risks of developing cancers of the blood and what testing should be done. If you develop or are likely to develop cancers of the blood, you should not use Tevagrastim, unless explicitly instructed to do so by your doctor.

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

Take special care with other products that stimulate white blood cells
Tevagrastim is one of a group of products that stimulate the production of white blood cells. Your doctor must always record the exact product you are using.

Other medicines and Tevagrastim
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist.

Pregnancy and breastfeeding
Tevagrastim has not been tested in pregnant or breastfeeding women.

Tevagrastim is not recommended during pregnancy.
It is important to tell your doctor if you:
- are pregnant or breastfeeding
- think you may be pregnant
- are planning to have a baby

If you become pregnant during Tevagrastim treatment, please inform your doctor.
Unless your doctor directs you otherwise, you must stop breastfeeding if you use Tevagrastim.

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

Important information about some of this medicine's ingredients
Tevagrastim contains 50 mg sorbitol in 1 ml of solution. A Tevagrastim 30 MIU/0.5 ml pre-filled syringe contains 25 mg of sorbitol. A 48 MIU/0.8 ml Tevagrastim pre-filled syringe contains 40 mg of sorbitol.

Sorbitol is a source of fructose. Do not take this medicine if you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder. Patients with hereditary fructose intolerance are not able to digest fructose, and this may cause severe side effects.
You must tell your doctor before you receive this medicine if you (or your child) have hereditary fructose intolerance or if your child is no longer able to consume sweet foods or drinks because of nausea, vomiting, or unpleasant effects such as bloating, abdominal cramps, or diarrhea.
This medicine contains less than 23 mg of sodium in one pre-filled syringe, and is therefore considered sodium free.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor 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.

Take this medicine at regular times as your doctor has told you.

How is Tevagrastim given and much should I take?
Tevagrastim 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.

Patients having a bone marrow transplant after chemotherapy:
You will normally receive your first dose of Tevagrastim 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 be taught how to give subcutaneous injections so that you can continue your treatment at home. However, do not attempt this unless you have been properly trained first by your health care provider.

Do not exceed the recommended dosage.

How long will I have to take Tevagrastim?
You will need to take Tevagrastim 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 Tevagrastim.

Tevagrastim is a single-use syringe.

If you have taken an overdose
Do not take a larger dose than the doctor prescribed you. 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 the medicine
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 a missed dose.

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

Do not take medicines in the dark! Check the label and dose every time you take 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

Like with all medicines, using Tevagrastim may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Important side effects:
Contact your doctor immediately if:
- You experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), rash, itchy rash (urticaria), swelling of the face, lips, mouth, tongue or throat (angioedema) and shortness of breath (dyspnea).
- You feel **upper left abdominal pain or pain in your left shoulder.** There have been reported cases of enlarged and ruptured spleen. Some cases of ruptured spleen were fatal.
- You experience a cough, fever and difficulty breathing (dyspnea) as these can be signs of acute respiratory distress syndrome (ARDS).
- You experience kidney injury (glomerulonephritis). Kidney injury has been seen in patients who received filgrastim. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown-colored urine or you notice you urinate less than usual.
- If you have any of the following or combination of the following side effects: swelling which may be associated with passing urine less frequently, difficulty breathing, abdominal swelling and feeling of abdominal fullness, and a general feeling of tiredness. These symptoms usually develop rapidly. They could be symptoms of a condition called capillary leak syndrome, which causes blood to leak from the small blood vessels into your body. This condition requires urgent medical attention.
- If you have a combination of any of the following symptoms:
  - fever, or shivering or feeling very cold, high 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 (blood poisoning), a severe infection with whole-body inflammatory response which can be life threatening and needs urgent medical attention.
  - if you get left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of your shoulder, as there may be a problem with your spleen (enlargement of the spleen or rupture of the spleen).
  - if you are being treated for severe chronic neutropenia and you have blood in your urine. Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine.

A common side effect of Tevagrastim use is pain in your bones or muscles, which can be relieved by taking standard pain relief medicines (analgesics).

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, ulcer and sores in your mouth, gut, liver, skin or your eyes, lungs, vagina and joints.

In normal stem cell donors an increase in white blood cells (leukocytosis) and a decrease of platelets may be seen; this reduces the ability of your blood to clot (thrombocytopenia). Your doctor will monitor these measures.

Additional side effects:

Very common (may affect more than 1 in 10 patients):
- decrease in level of platelets which reduces the ability of blood to clot (thrombocytopenia)
- low red blood cell count (anemia)
- headache
- diarrhea
- vomiting
- nausea
- unusual hair loss or thinning (alopecia)
- tiredness
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus (mucosal inflammation)
- fever

Common side effects (affect up to 1 in 10 patients):
- inflammation of the lung (bronchitis)
- upper respiratory tract infection
- urinary tract infection
- decreased appetite
- trouble sleeping (insomnia)
- dizziness
- reduced sense of touch, 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
- pain in your mouth and throat
- nose bleeds
- constipation
- oral pain
- enlargement of the liver (hepatomegaly)
- rash
- redness of the skin (erythema)
- muscle spasm
- pain when passing urine (dysuria)
- chest pain
- pain
- generalized weakness (asthenia)
- generally feeling unwell
- swelling in the hands and feet (peripheral edema)
- increase of certain enzymes in the blood
- changes in blood chemistry
- transfusion reaction

Uncommon side effects (affect up to 1 in 100 patients):
- increase in 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 (hyperuricemia)
- liver damage caused by blocking of the small veins within the liver
- 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
- bumpy skin rash (macuo-papular rash)
- disease which causes bones to become less dense, making them weaker and more brittle and (osteoporosis)
- injection site reaction

Rare side effects (affect up to 1 in 1,000 patients):
- 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 fluids which may result in puffiness (fluid volume disturbances)
- inflammation of the blood vessels in the skin
- purple, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweet's syndrome)
- worsening rheumatoid arthritis
- unusual change in the urine
- decrease in bone density
- inflammation of the aorta (the large blood vessel which transports blood from the heart to the body), see section 2
- formation of blood cells outside of the bone marrow (extramedullary hematopoiesis)

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 link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. 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 a doctor.

Do not use the medicine after the expiry date (expiry date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions:
Store this medicine in the refrigerator (2°C-8°C). Patients may store the medicine outside the refrigerator, below 25°C, for up to 5 days, but no later than the expiry date of the medicine. If the medicine has been stored outside the refrigerator, use it within 5 days or discard it. Do not put it back in the refrigerator.

Do not use this medicine if the solution in the syringe is cloudy or contains particles. Tevagrastim is a pre-filled syringe with needle safety guard and it is for single use only! If you have been prescribed a smaller dose than is present in the syringe, discard the rest after the injection!

Do not throw away medicines in the drain or in the garbage. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

6. Additional information

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

What the medicine looks like and contents of the pack
Tevagrastim is a clear and colorless solution.
Tevagrastim 30 MIU/0.5 ml: Each pre-filled syringe with needle safety guard contains 0.5 ml.
Tevagrastim 48 MIU/0.8 ml: Each pre-filled syringe with needle safety guard contains 0.8 ml.

Pack sizes:
Packs containing 1, 5 or 10 pre-filled syringes with needle safety guard, or a pack containing 10 (2 packs of 5 syringes) pre-filled syringes with needle safety guard.

Not all pack sizes may be marketed.

Name and address of registration holder and manufacturer:
Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020.

Revised in October 2024.

Registration number of the medicine in the Ministry of Health's National Drug Registry:
143.29.31990

Instructions on how to inject yourself with Tevagrastim pre-filled syringe with needle safety guard

General
This section contains information on how to give yourself an injection of Tevagrastim. Do not try to give yourself the injection unless you have received suitable training from your doctor or nurse. If you are not sure how to give the injection or you have any questions, consult your doctor or nurse.

The needle safety guard prevents needle stick injuries after you have used the syringe. It is important to throw away the used syringe in a puncture-proof disposal container.

How do I inject myself with Tevagrastim?
You will have to inject yourself into the tissue just under your skin. This is called a subcutaneous injection. You must inject Tevagrastim at about the same time every day.

Equipment you need
To give yourself a subcutaneous injection you will need:
- a Tevagrastim pre-filled syringe
- alcohol wipes or similar
- a puncture-proof disposal container that is used for safe disposal of used syringes (a biohazard waste container provided by the hospital or pharmacist)

What to do before you inject
1. Try to inject yourself at about the same time every day.
2. Take a Tevagrastim pre-filled syringe out of the refrigerator.
3. Check the expiry date on the syringe label (EXP). Do not use the syringe if the current date is later than the last day of the month listed on the label.
4. Check the appearance of Tevagrastim solution. The solution must be clear and colorless. Do not use the syringe if there are visible particles.
5. For a more comfortable injection, let the syringe stand for about 30 minutes so that it reaches room temperature, or hold it gently in your hand for a few minutes. Do not warm it in any other way (for example, do **not** warm it in the microwave or in hot water).
6. Do **not** remove the cover from the syringe until you are ready to inject.
7. **Wash your hands thoroughly.**
8. Find a comfortable and well-lit place. Place all the items you need for the injection within reach (the Tevagrastim pre-filled syringe, alcohol wipes, and puncture-proof disposal container).

How to prepare the injection
Before making the injection, follow these instructions:
1. Hold the syringe and carefully remove the needle cover without twisting. Pull horizontally (see Figures 1 and 2). Do not touch the needle or push the plunger.
2. You may notice small air bubbles in the pre-filled syringe. If there are air bubbles, tap the syringe gently with your fingers until the bubbles rise to the top of the syringe. Hold the syringe pointing up, and expel all the air by pushing the plunger up.
3. There is a scale on the syringe. Push the plunger up to the correct number of milliliters of Tevagrastim prescribed by your doctor.
4. Check again to make sure the correct dose of Tevagrastim is in the syringe.
5. Now the syringe is ready to be used.

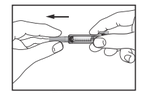
Figure 1

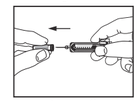
Figure 2

Where to inject?
The most suitable places for injecting yourself are:
- the top of the thighs,
- the abdomen area except for around your navel (see Figure 3).

If another person is injecting you, you can also have the injection in the back of your arms (see Figure 4).
It is advisable to change the injection site every day to avoid soreness in one place.

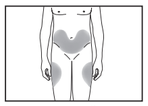
Figure 3

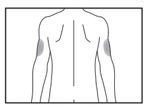
Figure 4

How to inject?
1. Disinfect the injection site with an alcohol wipe, and pinch the skin between your forefinger and thumb without squeezing (see Figure 5).
2. Insert the needle fully into the skin at a 45° angle, as you were shown by your doctor or nurse (see Figure 6).
3. Pull slightly on the plunger 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.
4. Keeping your skin pinched, depress the plunger slowly and evenly until the entire dose has been injected and the plunger cannot be depressed any further. Do not release the pressure on the plunger!
5. Inject only the dose your doctor has told you.
6. After injecting the liquid, remove the needle while maintaining pressure on the plunger and then let go of your skin
7. Let go of the plunger. The needle safety guard will quickly move to cover the needle (see Figure 7).

This is a single-use syringe. Do not use any Tevagrastim remaining in the syringe.

Important to remember
If you have any problem, ask your doctor or nurse for help.

Disposing of used syringes
- Throw away used syringes in the disposal container and keep the container out of the reach and sight of children.
- Dispose of the full disposal container as instructed by your doctor, nurse, or pharmacist.
- Do not throw away used syringes in your household waste.

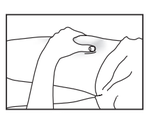
Figure 5

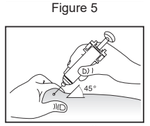

Figure 6

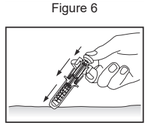
Figure 7

DOR-Tev-PIL-1024-12