Patient package insert in accordance with the pharmacists' regulations (preparations) - 1986
This medicine can be sold with a doctor's prescription only

StimoFil 300 mcg/0.5 ml
Solution for infusion or injection

Active ingredient and its concentration:
Each 0.5 ml contains:
Filgrastim 300 micrograms

StimoFil 480 mcg/0.5 ml
Solution for infusion or injection

Active ingredient and its concentration:
Each 0.5 ml contains:
Filgrastim 480 micrograms

For a list of inactive ingredients, please see section 6.

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

Please note, every time you collect your medicine at the pharmacy, it is important that you make sure that you always receive the same medicine your attending medical specialist prescribed for you. If the medicine you received appears different from the one you usually receive or the directions for use have changed, please refer to the pharmacist immediately to make sure you have received the correct medicine. Any switch or change in the dosage of a medicine containing filgrastim must be conducted by the attending medical specialist, Please check that the trade name of the medicine prescribed by your medical specialist is identical to the name of the medicine that you received from the pharmacist

1. What is the medicine intended for?

Stimofil is intended for:
- the reduction of the frequency and duration of neutropenia in patients treated with chemotherapy.
- the reduction of the duration of neutropenia in patients undergoing treatment prior to a bone marrow transplant.
- increasing the neutrophil count and reducing the frequency and duration of infections, in patients suffering from severe congenital chronic neutropenia or severe neutropenia of an unknown source and a history of severe infections, in long term administration.
- the treatment of patients suffering from persistent neutropenia with a progressive HIV infection in order to reduce the risk of bacterial infections where other measures of treating neutropenia are not suitable.
- for peripheral blood stem cell mobilization (stimulating stem cells to enter the blood stream to be collected and used in bone marrow transplantation).

Therapeutic group: Granulocytes (a type of white blood cells) growth factors (Granulocyte-colony stimulating factor).

StimoFil contains the active ingredient filgrastim. Filgrastim is a protein produced in bacteria called Escherichia coli by recombinant DNA technology. It belongs to a group of proteins called cytokines and is very similar to a natural protein (granulocyte-colony stimulating factor [G-CSF]) produced by your own body Filgrastim stimulates the bone marrow (the tissue where new blood cells are made) to produce more white blood cells that help fight infection.

2. Before using the medicine

Do not use the medicine if:

- you are hypersensitive (allergic) to the active ingredient filgrastim or to any of the other ingredients this medicine contains (see section 6).

Special warnings regarding the use of this medicine

- **Before the treatment with StimoFil, tell the doctor if:**
  - you suffer from sickle cell anaemia; StimoFil may cause sickle cell crisis
  - you suffer from Osteoporosis (bone disease)
- **During treatment with StimoFil, tell your doctor immediately if:**
  - you get left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of enlarge spleen (splenomegaly) or possibly rupture of 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).
  - you have sudden signs of allergy such as rash, itching or hives of 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 severe allergic reaction.
  - 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).
- The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex) which may cause an allergic reaction.
- 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 of the inflammation can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell the doctor if you experience these symptoms.

Loss of response to filgrastim
If you experience a loss of response or failure to maintain the response to filgrastim treatment, your doctor will investigate the reasons why, including whether you have developed antibodies which neutralise filgrastim's activity.
Your doctor may want to monitor your condition closely (see section 4 "side effects") .
If you suffer from severe chronic neutropenia, you may be at risk of developing cancer of the blood [leukaemia, myelodysplastic syndrome (MDS)]. You should consult the doctor about your risks of developing cancer of the blood and what follow-up tests you should perform. If you develop or are likely to develop cancer of the blood, you should not use StimoFil, unless instructed by your doctor.
If you are a stem cell donor, you must be between the ages 16 and 60 years.

Take special care with other products that stimulate production of white blood cells
StimoFil is one of a group of products that stimulate the production of white blood cells. The attending doctor should always record the exact product you are using.

Drug interactions

If you are taking, or have recently taken other medicines, including non-prescription drugs and nutritional supplements, tell the doctor or pharmacist.
You should not use StimoFil in the 24 hours before and the 24 hours after receiving chemotherapy.

Pregnancy and breast-feeding

This medicine has not been tested in pregnant women. It is important to tell your doctor if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby. This medicine is not recommeded for use during pregnancy.
It is unknown whether the medicune passes over into the breast milk, therefore, your doctor may decide that you should not use this medicine if you are breast-feeding.

Driving and use of machinery

StimoFil 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 taking StimoFil and before driving or operating machinery.

Important information about some of the ingredients of the medicine

- This medicine contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars (fructose), contact your doctor before using this medicine.
- This medicine contains less than 1 mmol sodium (0.035 mg) per dose, therefore it is considered "sodium-free".

3. How should you use the medicine?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about the dosage and treatment regimen.
The dosage and treatment regimen will be determined by the doctor only, depending on the condition for which you are taking StimoFil and on your bodyweight.
Do not exceed the recommended dose.

Method of administration
This medicine is given by injection in one of the following ways: through an intravenous (IV) infusion (drip) or by a subcutaneous (SC) injection (into the tissue just under the skin).

If you are receiving this medicine by subcutaneous injection, your doctor may suggest that you learn how to inject yourself the medicine. Your doctor or nurse will explain how to carry this out (see information below on instructions for injecting yourself). Do not attempt to inject yourself without this training. Some of the information required is given below, but proper treatment of your disease requires close supervision and constant cooperation with your doctor.

Information for injecting yourself

This section contains information on how to inject yourself. Do not try to inject yourself the medicine unless you have received special training from your doctor or nurse. If you are not sure about injecting yourself or you have any questions, refer to your doctor or nurse for help.

How do you inject StimoFil to yourself?

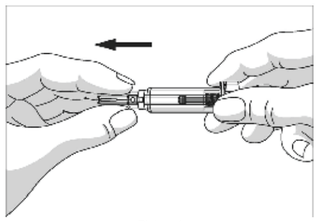
You will need to inject yourself the medicine into the tissue just under the skin (subcutaneous injection). The injection should be performed every day at the same time.

Equipment that you need

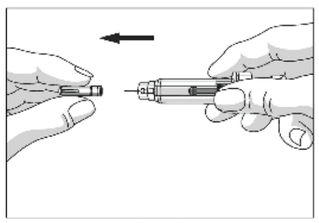
To give yourself a subcutaneous injection you will need:
- a pre-filled syringe of StimoFil
- alcohol swab or similar disinfectant

What should you do before giving yourself a subcutaneous injection of StimoFil?
Ensure the needle cover remains on the syringe until just before you are ready to inject.
a. Take the StimoFil pre-filled syringe out of the refrigerator.
b. Check the expiry date which appears 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 has been kept outside of the refrigerator for more than 15 days.
c. Check the appearance of the 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, let the pre-filled syringe stay 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 everything you need where you can reach them (the pre-filled syringe and alcohol swab).

How do you prepare the StimoFil syringe?
Before you inject the medicine, you must do the following actions:
1. Hold the syringe and gently take the cover from the needle without twisting. Pull straight as shown in pictures 1 and
2. Do not touch the needle or push the plunger.



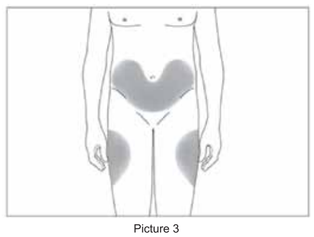
Picture 1



Picture 2

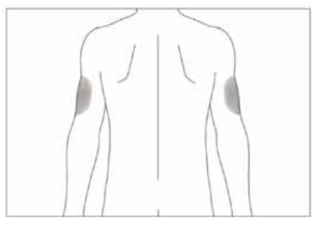
2. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before the injection. Injecting the solution with the air bubble is harmless.
3. The syringe may contain more liquid than you need. Use the scale on the syringe to set the correct dose of StimoFil that your doctor prescribed. Eject unnecessary liquid by pushing the plunger to the number (mL) on the syringe that matches the prescribed dose.
4. Check again to make sure the correct dose of StimoFil is in the syringe.
5. You can now use the pre-filled syringe.

Where should you inject the medicine?
The most suitable places to inject yourself are:
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).



Picture 3

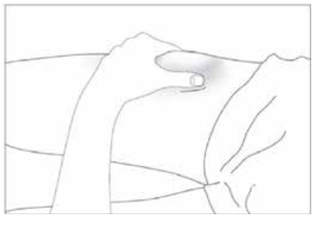
If someone else is injecting the medicine to you, he can also inject in the back of your arms (see picture 4).



Picture 4

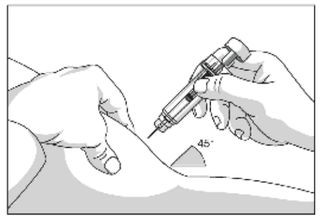
It is recommended to change the injection site every day to avoid the risk of soreness at one place.

How should you inject the medicine?
a. Disinfect the injection site by using an alcohol swab and pinch the skin (without squeezing it) between your thumb and forefinger (see picture 5).

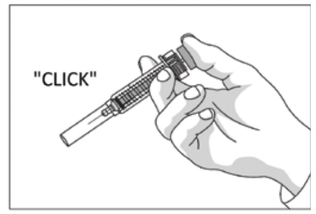


Picture 5

b. Insert the needle fully into the skin, as shown by your doctor or nurse (see picture 6).
c. 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.
d. Inject the dose prescribed by your doctor only, according to the instructions below.
e. Keep the skin pinched the whole time, press the plunger slowly and at a steady pace while grasping the finger flange until the entire dose has been injected and the plunger cannot be pressed any further. Do not release the pressure on the plunger!
f. After injecting the liquid, remove the needle while keeping the syringe at the same angle and maintaining pressure on the plunger, then, release the skin. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm the shield activation (see picture 7). The needle safety guard will not be activated unless the entire dose has been injected.



Picture 6



Picture 7

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

Disposing of used syringes

The needle safety guard prevents needle stick injuries after use, therefore there are no special instructions for disposal required. Dispose of the syringe as instructed by your doctor, nurse or pharmacist.

If you have accedently injected a higher dosage refer to your doctor or pharmacist as soon as possible, and bring the package of the medicine with you.

If you forget to inject this medicine at the set time, do not inject a double dose to compensate for a forgotten one. Refer to your doctor to discuss when you should inject the next dose.

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

If you stop using the medicine

The doctor will tell you when to stop using the medicine. It is possible that a number of treatment courses with StimoFil will be required.

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

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

4. Side effects

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

Refer to the doctor immediately if during treatment:
- you experience an allergic reaction including weakness, a 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 (dyspnoea). Hypersensitivity is common in patients with cancer
- you experience a cough, fever and difficulty breathing (dyspnoea). These may be signs of Acute Respiratory Distress Syndrome (ARDS). This syndrome is uncommon in patients with cancer.
- you suffer from pain in the upper left part of your belly (abdonimal pain), pain below the left rib cage or at the tip of your left shoulder since these may relate 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 (haematuria). Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine (proteinuria).
- you suffer from any of the following side effects or a combination of them: swelling or puffiness which may be associated with urinating 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 an uncommon condition (may appear in up to 1 in 100 users) called Capillary Leak Syndrome which causes the blood to leak from the small blood vessels into the body and requires urgent medical attention.

- If you experience a combination of any of the following symptoms:
  - fever or shivering, or feeling very cold, rapid 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", a severe infection with a whole-body inflammatory response which can be life threatening and requires urgent medical attention.

If you suffer from a kidney injury (glomerulonephritis). Kidney injury has been observed in patients who received StimoFil. Refer to your doctor immediately 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.

Additional side effecs
A very frequent side effect of StimoFil use is pain in your muscles or bones musculoskeletal pain). This side effect can be alleviated 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 the hands and soles of the feet and ulcer and sores in the mouth, gut, liver, skin, eyes, lungs, vagina and joints. An increase in white blood cells count (leukocytosis) and a decrease in platelets count which reduces the ability of blood to clot (thrombocytopenia) are very common in normal stem cells donors - these will be monitored by your doctor.

Very common side effects (effects that appear in more than 1 in 10 users):
- vomiting
- nausea
- unusual hair loss or thinning (alopecia)
- tiredness (fatigue)
- soreness and swelling of the digestive tract lining - from the mouth to the anus (mucosal inflammation)
- decrease in platelets count which reduces the ability of blood to clot (thrombocytopenia)
- low red blood cell count (anaemia)
- fever (pyrexia)
- headache
- diarrhoea

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

Uncommon side effects (side effects that appear in 1-10 out of 1,000 users):
- 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 (hyperuricaemia)
- 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 oedema)
- inflammation of the lungs (interstitial lung disease)
- abnormal lung x-rays
- bleeding from the lung (pulmonary haemorrhage)
- lack of oxygen absorption in the lung (hypoxia)
- bumpy skin rash (rash macuo-papular)
- a disease which causes bones to become less dense, making them weaker, more brittle and likely to break (osteoporosis)
- injection site reaction

Rare side effects (side effects that appear in 1-10 out of 10,000 users):
- Inflammation of the aorta (see section 2).
- severe pain in the bones, chest, gut or joints (sickle cell anaemia 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 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 occasionaly the face and neck with a fever (Sweet's syndrome)
- worsening of rheumatoid arthritis
- unusual change in the urine
- decreased bone density

If a side effect occurs, if one of the side effects worsenes, or when you suffer from a side effect not mentioned in the leaflet, consult the doctor.

Reporting of side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Reporting side effects following drug treatment" found in the Ministry of Healthe 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 any other medicine must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed by the doctor.
- Do not use the medicine after the expiry date (exp. date) which appears on the package and on the pre-filled syringe label. 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 (at a temperature not exceeding 25°C) one time for a period of up to 15 days, or until the expiry date which appears on the package, whichever comes first. At the end of this period, the syringe should not be returned to the refrigerator, it should be disposed of.
- Store in the original package in order to protect from light.
- Do not use the medicine if the liquid seems turbid, its color has changed or it contains particles. Do not shake.
- Medicines should not be disposed of via wastewater or household waste. Dispose of the syringe as instructed 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, the medicine also contains:

D-Sorbitol, glacial acetic acid, sodium hydroxide, polysorbate 80, water for injection

What the medicine looks like and the content of the package:

StimoFil is a clear colorless solution in a pre-filled syringe, indicated with scale markings of 1/40 from 0.1 ml to 1 ml, with 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 an individual blister pack.
Not all pack sizes may be marketed.

Registration Holder and Address: Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Petach-Tikva.

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

Drug registration number at the national medicines registry of the Ministry of Health:
StimoFil 300 mcg/0.5 ml: 164-19-36445
StimoFil 480 mcg/0.5 ml: 164-20-36446

This leaflet was checked and approved by the Ministry of Health in November 2019.

StimoFIL 300 & 480 PILPB0220-08