

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS
(PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only.

Neupogen 30 MU Pre-filled syringe
Neupogen 48 MU Pre-filled syringe
Neupogen 30 MU Vials
for intravenous/subcutaneous administration

Composition:

Each **Neupogen** 30 MU syringe contains 30 million units (300 micrograms (mcg)) of filgrastim in 0.5 ml (0.6 mg/ml).

Each **Neupogen** 48 MU syringe contains 48 million units (480 micrograms (mcg)) of filgrastim in 0.5 ml (0.96 mg/ml).

Each **Neupogen** 30 MU vial contains 30 million units (300 micrograms (mcg)) of filgrastim in 1 ml (0.3 mg/ml).

For inactive ingredients and allergens in the medicine – see section 6 “Further information”

Read all of this leaflet carefully and until the end before using this medicine. This leaflet contains concise information about the medicine. If you have further questions, contact your doctor, nurse or pharmacist.

- Keep this leaflet. You may need to read it again.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

Important information for your attention

- You can inject **Neupogen** 30 MU pre-filled syringe, **Neupogen** 48 MU pre-filled syringe yourself in your home after receiving instructions from your healthcare professional. Please carefully read the instructions for self-injection of **Neupogen** pre-filled syringe that appear at the end of this leaflet.
- Injecting **Neupogen** 30 MU vials is done by a healthcare professional staff only.
- Strict adherence to the doctor's instructions (dosage, injection times and duration of treatment) increases the chance of treatment success. In any case, do not discontinue the treatment without consulting the attending doctor. Please read sections 2 and 4 for expanded safety information.
- During treatment regular blood tests should be performed.
- Keep **Neupogen** in the refrigerator (see section 5).
- **Neupogen** is intended for single use!

1. WHAT IS THE MEDICINE INTENDED FOR?

Neupogen 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.

Neupogen 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 infection.

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

Neupogen 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.

Therapeutic group: Cytokines

2. BEFORE USING THIS MEDICINE

X Do not use Neupogen if:

- you are sensitive (allergic) to filgrastim or any of the other ingredients of this medicine (listed in section 6 – “Further information”).

! Special warnings regarding the usage of the medicine

Talk to your doctor, pharmacist or nurse before using **Neupogen**.

Please tell your doctor before starting treatment if you have:

- sickle cell anemia, as **Neupogen** may cause sickle cell crisis.
- 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.
- osteoporosis (bone disease).

Please tell your doctor immediately during treatment with **Neupogen** 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).
- experience puffiness in your face or ankles, blood in your urine or brown-colored urine or you notice you urinate less than usual (glomerulonephritis).
- 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 an enlarged spleen [splenomegaly], or possibly rupture of the spleen).
- 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 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 can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience those symptoms.

Children and adolescents

Neupogen 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.

Tests and follow-up

If you suffer from severe chronic neutropenia, it is recommended that during treatment with **Neupogen**, 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 of the patient 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 **Neupogen**, unless instructed 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

Neupogen is one of a group of products that stimulate the production of white blood cells. Your healthcare professional should always record the exact product you are using.

Other medicines and Neupogen

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including non-prescription medicines and nutritional supplements.

Do not start treatment with **Neupogen** from 24 hours before and until 24 hours after receiving chemotherapy.

Pregnancy and breast-feeding

Neupogen has not been tested in pregnant or breast-feeding women.

Neupogen is not recommended during pregnancy.

If you are pregnant, breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you become pregnant during **Neupogen** treatment, please inform your doctor.

Unless your doctor directs you otherwise, you must stop breast-feeding if you use **Neupogen**.

Driving and using machines

Neupogen 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 **Neupogen** and before driving or operating machinery.

Important information about some of the ingredients of this medicine

Neupogen contains sodium

Neupogen contains less than 1 mmol (23 mg) sodium per 0.3/ 0.6/ 0.96 mg/ml, that is to say essentially 'sodium free'.

Neupogen contains sorbitol

This medicine contains 50 mg sorbitol in each ml.

Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) 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 (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhea.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure regarding the dosage and how to use the medicine.

The dosage and treatment regimen will be determined by the doctor only.

How is Neupogen given and how much should I take?

Neupogen 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 **Neupogen** 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, you should not attempt this unless you have been properly trained first by your healthcare provider.

Do not exceed the recommended dose

How long will I have to take Neupogen?

You will need to take **Neupogen** 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 **Neupogen**.

If you accidentally use a higher dosage

Do not increase the dose your doctor has given you. If you think you have injected more than you should, contact your doctor as soon as possible.

If you took an overdose or if a child accidentally swallowed the medicine, refer to the doctor or proceed to a hospital emergency room immediately and bring the package of the medicine with you.

If you forget to use Neupogen

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 recommended by the doctor.

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

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

4. SIDE EFFECTS

As with any medicine, use of **Neupogen** 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.

Refer to the doctor immediately if you notice any of the following effects:

- if 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).
- if you experience a cough, fever and difficulty breathing (dyspnea), as this can be a sign of Acute Respiratory Distress Syndrome (ARDS).
- if you experience kidney injury (glomerulonephritis). Kidney injury has been seen in patients who received **Neupogen**. 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 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 in a rapid fashion.
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 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” (also called "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 [splenomegaly] or rupture of the spleen).
- if 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 experience this side effect or if protein is found in your urine (proteinuria).

A very common side effect of **Neupogen** use is pain in your muscles or bones (musculoskeletal pain), which can be helped 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 and 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), these will be monitored by your doctor.

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

- decrease 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 (fatigue)
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus (mucosal inflammation)
- fever (pyrexia)

Common side effects (occur in 1 – 10 out of 100 treated patients):

- inflammation of the lung (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 (erythema)
- 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 (occur in 1 – 10 out of 1000 treated patients):

- increase in white blood cells (leukocytosis)
- allergic reaction (hypersensitivity)
- rejection of transplanted bone marrow (graft versus host disease = GvHD)
- high uric acid levels in the blood, which may cause gout (hyperuricemia) (blood uric acid increased)
- 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 (pulmonary hemorrhage)
- lack of absorption of oxygen in the lung (hypoxia)
- bumpy skin rash (rash maculo-papular)
- disease which causes bones to become less dense, making them weaker, more brittle and likely to break (osteoporosis)
- injection site reaction

Rare side effects (occur in 1 – 10 out of 10,000 treated 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 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 (Sweet's syndrome)
- worsening of rheumatoid arthritis
- unusual change in the urine
- bone density decreased
- Inflammation of aorta (the large blood vessel which transports blood from the heart to the body), see section 2

If you get any side effects, if one of the side effects is worsening, if you suffer from a side effect not listed in the leaflet, you should consult with a 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://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.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 a doctor.
- Store in a refrigerator (2°C-8°C). Do not freeze. Keep the container in the outer carton in order to protect from light.
- Do not use this medicine after the expiry date (Exp. Date) which is stated on the syringe or vial and carton. The expiry date refers to the last day of that month.
- Do not use this medicine if you notice discoloration, cloudiness or particles, it should be a clear, colorless liquid.
- **Neupogen is intended for single use! If you have been prescribed a lower dose than the amount in the syringe or vial, destroy the remainder after the injection!**
- 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, this medicine also contains:

Sorbitol, Glacial acetic acid, Polysorbate 80, Sodium hydroxide 1N ad pH 4, water for injection.

The medicine contains less than 1 mmol (23 mg) of sodium in 0.3/0.6/0.96 mg/ml of solution.

The medicine contains approx. 50 mg of sorbitol per 1 ml of solution.

What does the medicine look like and what are the contents of the package?

Neupogen is a clear, colorless solution intended for subcutaneous injection or for intravenous infusion.

Neupogen is available in vials or in a pre-filled syringe with a separate needle.

Neupogen 30 MU Vials – 30 MU/1 ml is marketed in a package containing five vials.

Neupogen 30 MU pre-filled syringe - 30 MU/0.5 ml is marketed in a package containing 1 or 5 syringes*.

Neupogen 48 MU pre-filled syringe - 48 MU/0.5 ml is marketed in a package containing 1 or 5 syringes*.

*Not all pack sizes may be available.

Manufacturer: Amgen Europe B.V., Breda, the Netherlands.

Registration Holder: Amgen Europe B.V., P.O. BOX 53313, Tel - Aviv.

This leaflet was checked and approved by the Ministry of Health in August 2015 and was updated according to the guidelines of the Ministry of Health in May 2019.

Registration number of the medicine in the National Drugs Registry at the Ministry of Health

Neupogen 30 MU pre-filled syringe: 117 22 29875

Neupogen 48 MU pre-filled syringe: 117 21 29876

Neupogen 30 MU vials: 058 31 27318

INSTRUCTIONS FOR SUBCUTANEOUS SELF-INJECTION OF NEUPOGEN PRE-FILLED SYRINGE:

Instructions for injecting:

Neupogen 30 MU pre-filled syringe

Neupogen 48 MU pre-filled syringe

This section contains information on how to give an injection of **Neupogen pre-filled syringe**.

Important: do not try to give yourself an injection unless you have received training from your doctor or nurse.

Injecting **Neupogen** vial is done by a healthcare professional staff only.

Neupogen is injected into the tissue just under the skin.

This is known as a subcutaneous injection.

Equipment that you need

To give yourself a subcutaneous injection you will need:

- a new pre-filled syringe of **Neupogen**,
- alcohol wipes or similar.

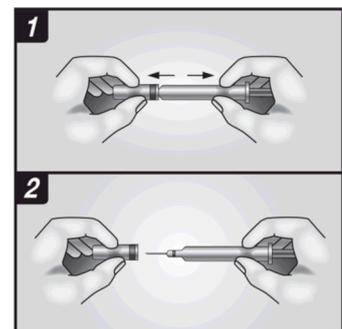
What do I do before I give myself a subcutaneous injection of Neupogen?

1. Remove one tray containing a syringe from the refrigerator and leave at room temperature for approximately 30 minutes or hold gently in your hand for a few minutes. This will make the injection more comfortable. **Do not** warm **Neupogen** in any other way (for example, do not warm it in a microwave or in hot water).
2. Do not shake the pre-filled syringe.
3. Place the tray in your hand and peel the paper off the tray.
4. Flip the tray to place the pre-filled syringe onto your palm.
5. **Do not** remove the needle cover until you are ready to inject.
6. Check the expiry date on the pre-filled syringe label (EXP). Do not use it if the date has passed the last day of the month shown.
7. Check the appearance of **Neupogen**. It must be a clear and colorless liquid. If there is discoloration, cloudiness or particles in it, you must not use it.
8. **Wash your hands thoroughly.**
9. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

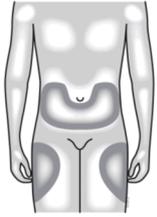
How do I prepare my Neupogen injection?

Before you inject **Neupogen** you must do the following:

1. To avoid bending the needle, securely grasp the pre-filled syringe by the glass barrel. Gently pull the cover from the needle without twisting as shown in pictures 1 and 2.
2. Do not touch the needle or push the plunger.
3. 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.



4. You can now use the pre-filled syringe.



Where do I give my injection?

The best places to inject are the top of your thighs and the abdomen. If someone else is injecting you, they can also use the back of your arms.

You may change the injection site if you notice the area is red or sore.

How do I give my injection?

1. Disinfect your skin by using an alcohol wipe and pinch (without squeezing) the skin between your thumb and forefinger.
2. Put the needle fully into the skin as shown by your nurse or doctor.
3. Push the plunger with a slow constant pressure, always keeping your skin pinched, until the syringe is empty.
4. Remove the needle and let go of your skin.
5. If you notice a spot of blood you may gently dab it away with a cotton ball or tissue. Do not rub the injection site. If needed, you may cover the injection site with a plaster.
6. Only use each syringe for one injection. Do not use any **Neupogen** that may be left in the syringe.

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

Disposing of used syringes

- Do not put the cover back on used needles, as you may accidentally prick yourself.
- Keep used syringes out of the sight and reach of children.
- Syringes should not be thrown out in the household rubbish. Your pharmacist will know how to dispose of used syringes or syringes no longer needed.