Package leaflet: Information for the user

Nivestim 12 MU/0.2 ml solution for injection/infusion
Nivestim 30 MU/0.5 ml solution for injection/infusion
Nivestim 48 MU/0.5 ml solution for injection/infusion
filgrastim

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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.

What is in this leaflet

1. What Nivestim is and what it is used for
2. What you need to know before you use Nivestim
3. How to use Nivestim
4. Possible side effects
5. How to store Nivestim
6. Contents of the pack and other information

1. What Nivestim is and what it is used for

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

Nivestim 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 to help prevent infections;
- in patients with advanced HIV infection which will help reduce the risk of infections.

2. What you need to know before you use Nivestim

Do not use Nivestim
- if you are allergic to filgrastim or any of the other ingredients of this medicine (listed in section 6)**.**

Warnings and precautions

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

Please tell your doctor before starting treatment **if you have**:
- sickle cell anaemia, as Nivestim may cause sickle cell crisis.
- osteoporosis (bone disease).

Please tell your doctor immediately during treatment with Nivestim, 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-coloured 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 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 can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience these symptoms.

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 neutralise 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 (leukaemia, 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 Nivestim, 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

Nivestim 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 Nivestim

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

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

Nivestim is not recommended during pregnancy.

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.

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

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

Driving and using machines

Nivestim 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 Nivestim and before driving or operating machinery.

Nivestim contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 0.6 mg/ml or 0.96 mg/ml dose, that is to say essentially 'sodium-free'.

Nivestim 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 diarrhoea.

3. How to use Nivestim

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

How is Nivestim given and how much should I take?

Nivestim 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 Nivestim you should take.

Patients having a bone marrow transplant after chemotherapy:
You will normally receive your first dose of Nivestim 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.

How long will I have to take Nivestim?

You will need to take Nivestim 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 Nivestim.

Use in children

Nivestim 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.

If you use more Nivestim than you should
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 forget to use Nivestim

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.

If you have any further questions on the use of this product, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor immediately during treatment:
- 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 (dyspnoea).
- if you experience a cough, fever and difficulty breathing (dyspnoea) 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 filgrastim. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown-coloured 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 (haematuria). Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine (proteinuria).

A common side effect of filgrastim 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 (leucocytosis) 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 (may affect more than 1 in 10 people):

- decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
- low red blood cell count (anaemia)
- headache
- diarrhoea
- 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 (may affect up to 1 in 10 people):
- 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 (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
- oral pain
- 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 (oedema peripheral)
- increase of certain enzymes in the blood
- changes in blood chemistry
- transfusion reaction

Uncommon side effects (may affect up to 1 in 100 people):
- increase in white blood cells (leucocytosis)
- allergic reaction (hypersensitivity)
- rejection of transplanted bone marrow (graft versus host disease)
- high uric acid levels in the blood, which may cause gout (hyperuricaemia) (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 oedema)
- inflammation of the lungs (interstitial lung disease)
- abnormal x-rays of the lungs (lung infiltration)

- bleeding from the lung (pulmonary haemorrhage)
- 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 (may affect up to 1 in 1,000 people):
- 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-coloured, 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
- inflammation of the aorta (the large blood vessel which transports blood from the heart to the body), see section 2

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517;
Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Malta
ADR Reporting
Website:
www.medicinesauthority.gov.mt/adrportal

5. How to store Nivestim

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the pre-filled syringe after EXP. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C – 8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light.

The syringe can be removed from the refrigerator and left at room temperature for a single period of maximum 15 days (but not above 25°C).

Do not use this medicine if you notice it is cloudy or there are particles in it.

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. Contents of the pack and other information

What Nivestim contains

- The active substance is filgrastim. Each ml contains 60 million units [MU] (600 μg) or 96 million units [MU] (960 μg) of filgrastim.
- Nivestim 12 MU/0.2 ml solution for injection/infusion: each pre-filled syringe contains 12 million units (MU), 120 μg of filgrastim in 0.2 ml (corresponding to 0.6 mg/ml).
- Nivestim 30 MU/0.5 ml solution for injection/infusion: each pre-filled syringe contains 30 million units (MU), 300 μg of filgrastim in 0.5 ml (corresponding to 0.6 mg/ml).
- Nivestim 48 MU/0.5 ml solution for injection/infusion: each pre-filled syringe contains 48 million units (MU), 480 μg of filgrastim in 0.5 ml (corresponding to 0.96 mg/ml).
- The other ingredients are acetic acid (glacial), sodium hydroxide, sorbitol E420, polysorbate 80, and water for injections.

What Nivestim looks like and contents of the pack

Nivestim is a clear colourless solution for injection/infusion in a glass pre-filled syringe with an injection needle (stainless steel) with a needle guard. The needle cover contains epoxyprene, a derivative of natural rubber latex which may come into contact with the needle.

There are 1, 5, 8 or 10 syringes in each pack. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer

Hospira Zagreb d.o.o.
Prudnička cesta 60
10291 Prigorje Brdovečko
Croatia

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Ireland
Pfizer Healthcare Ireland
Tel: 1800 633 363 (toll free)
+44 (0) 1304 616161

United Kingdom
Hospira UK Limited
Tel: + 44 (0) 1628 515500

Malta
Drugsales Ltd
Tel: +356 21 419 070/1/2

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Ref: bNT 11_0

Information on self administration by the patient

This section contains information on how to give yourself an injection of Nivestim. It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. It is also important that you dispose of the syringe in a puncture-proof container. If you are not sure about giving yourself the injection or you have any questions, please ask your doctor or nurse for help.

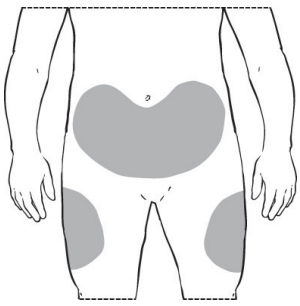
How do I administer my Nivestim?

Nivestim is usually given once a day by injection, usually into the tissue just under the skin. This is known as a subcutaneous injection.

Learning to give your own injections will mean that you will not have to wait at home for a nurse to call, nor will you have to go to the hospital or clinic every day to receive your injections.

You will need to have your injections at about the same time every day. The most suitable places for injection are:

- the front of the thighs,
- the abdomen, except for the area around the navel.



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

Equipment required for administration

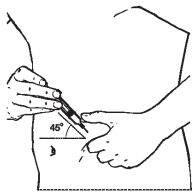
To give yourself a subcutaneous injection you will need the following items:

- A new pre-filled syringe of Nivestim.
- A sharps container (puncture proof container) for disposing of used syringes safely.
- Antiseptic wipes (if recommended by your doctor or nurse).

How do I give my subcutaneous Nivestim injection?

1. Try to self-inject at approximately the same time every day.

2. Remove the Nivestim syringe from the fridge and allow it to reach room temperature (approximately 25 °C). This will take 15–30 minutes. Check the date on the pack to make sure that the medicine has not passed the expiry date. Make sure you have your sharps container nearby.
3. Find a comfortable well lit working place to give your injection and check the dose that you have been prescribed.
4. Wash your hands thoroughly with soap and water.
5. Remove the syringe from the blister pack and check that the solution is clear, colourless and practically free from visible particles. Do not use the Nivestim syringe if the liquid has particles floating in it or any of the liquid has leaked out of the syringe.
6. Hold the syringe with the needle pointing upwards. Remove the protective cap from the injection needle. The syringe is now ready for use. You may notice a small air bubble in the syringe. You do not have to remove the air bubble before injecting. Injecting the solution with an air bubble present is harmless.
7. Decide where to inject Nivestim - find a place on the front of your abdomen or the front of your thigh. Choose a different injection site each time. Do not choose an area which is tender, red, bruised or scarred. If your nurse or doctor recommends it, clean the area of skin with an antiseptic wipe.
8. Pinch a large area of skin, taking care not to touch the area you have cleaned.
9. With your other hand, insert the needle at an approximate 45˚ angle.



10. Pull the plunger back slightly to check if any blood appears in the syringe. If you do see blood inside the syringe, remove the needle and re-insert it in a different site. Slowly push down the plunger until all the contents of the syringe have been emptied.
11. After injecting the solution remove the needle from the skin.
12. Ensure the needle guard covers the needle according to the instructions for active needle guard or passive needle guard below.
13. Place the syringe into the sharps container. Do not try to replace the protective cap.

- Keep used syringes out of the reach and sight of children
- NEVER put used syringes into your normal household waste bin.

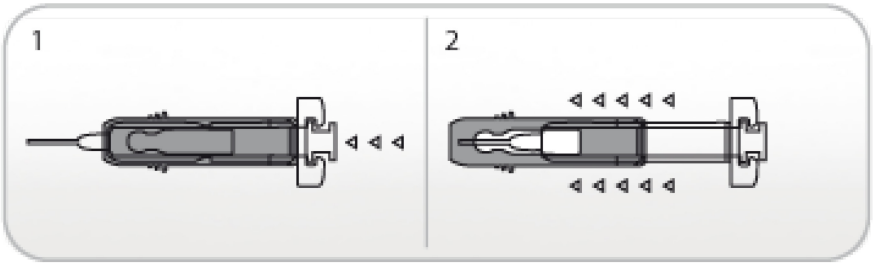
Remember

Most people can learn to give themselves a subcutaneous injection, but if you are experiencing a lot of difficulty, please do not be afraid to ask for help and advice from your doctor or nurse.

***Use of Active UltraSafe Needle Guard for* Nivestim 12 MU/0.2 ml solution for injection/infusion**

The pre-filled syringe has an UltraSafe Needle Guard attached in order to protect from needle stick injury. When handling the pre-filled syringe, keep hands behind the needle.

1. Perform the injection using the technique described above.
2. When you have completed the injection, slide the needle guard forward until the needle is completely covered (device ‘clicks’ into place).

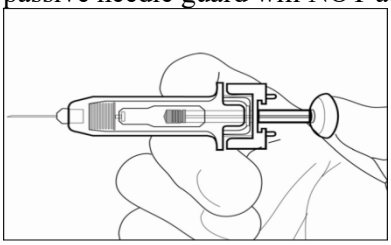


Use of UltraSafe Passive Needle Guard for **Nivestim 30 MU/0.5 ml solution for injection/infusion and Nivestim 48 MU/0.5 ml solution for injection/infusion**

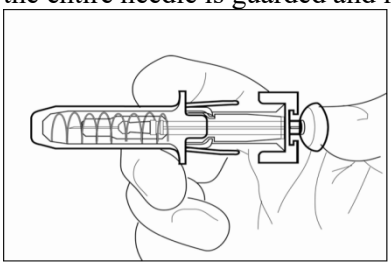
The pre-filled syringe has an UltraSafe Needle Guard attached in order to protect from needle stick injury. When handling the pre-filled syringe, keep hands behind the needle.

1. Perform the injection using the technique described above.

2. Depress the plunger while grasping the finger flange until the entire dose has been given. The passive needle guard will NOT activate unless the ENTIRE dose has been given.



3. Remove the needle from your skin, then let go of the plunger and allow the syringe to move up until the entire needle is guarded and locks into place.



THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY:

Nivestim does not contain any preservative. In view of the possible risk of microbial contamination, Nivestim syringes are for single use only.

Accidental exposure to freezing temperatures for up to 24 hours does not affect the stability of Nivestim. The frozen pre-filled syringes can be thawed and then refrigerated for future use. If exposure has been greater than 24 hours or frozen more than once, then Nivestim should NOT be used.

Nivestim must not be diluted with sodium chloride solution. This medicinal product must not be mixed with other medicinal products except those mentioned below. Diluted filgrastim may be adsorbed to glass and plastic materials except diluted, as mentioned below.

If required, Nivestim may be diluted in 5% glucose solution. Dilution to a final concentration less than 0.2 MU (2 μg) per ml is not recommended at any time. The solution should be visually inspected prior to use. Only clear solutions without particles should be used. For patients treated with filgrastim diluted to concentrations below 1.5 MU (15 μg) per ml, human serum albumin (HSA) should be added to a final concentration of 2 mg/ml.

Example: In a final injection volume of 20 ml, total doses of filgrastim less than 30 MU (300 μg) should be given with 0.2 ml of 200 mg/ml (20%) human albumin solution added. When diluted in 5% glucose solution, Nivestim is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

After dilution: Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2 °C to 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.