PACKAGE LEAFLET: INFORMATION FOR THE USER

Accofil 48 MU/0.5 ml (0.96 mg/ml) solution for injection/infusion in pre-filled syringe
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 Accofil is and what it is used for
2. What you need to know before you use Accofil
3. How to use Accofil
4. Possible side effects
5. How to store Accofil
6. Contents of the pack and other information

1. What Accofil is and what it is used for

What Accofil is

Accofil is a white blood cell growth factor (granulocyte-colony stimulating factor) and belong 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. Accofil 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. Accofil stimulates the bone marrow to produce new white cells quickly.

Accofil 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;
- 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 Accofil

Do not use Accofil

- 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 Accofil:

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

Please tell your doctor immediately during treatment with Accofil, 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).
- 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).
- 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 a signs of 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).
- Have symptoms of inflammation of the aorta (the large blood vessel which transports blood from the heart to the body), this has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if youexperience 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 Accofil, unless instructed by your doctor.

If you are a stem cell donor, you must be aged between16 and 60 years.

Take special care with other products that stimulate white blood cells
Accofil 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 Accofil

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

Pregnancy and breast-feeding

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

Accofil 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 Accofil treatment, please inform your doctor.

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

Driving and using machines

Accofil 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 Accofil and before driving or operating machinery.

Accofil contains sodium
This medicine contains less than 1 mmol (23 mg) sodium per pre-filled syringe, that is to say essentially 'sodium free'.

Accofil contains sorbitol
This medicine contains 50mg 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.

An allergy to natural rubber (latex). The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex) which may cause severe allergic reaction.

3. How to use Accofil

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

How is Accofil given and how much should I take?
Accofil 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 Accofil you should take.

Patients having a bone marrow transplant after chemotherapy:
You will normally receive your first dose of Accofil 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 health care provider.

How long will I have to take Accofil?

You will need to take Accofil 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 Accofil.

Use in children

Accofil 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.

Information for injecting yourself
This section contains information on how to give yourself an injection of Accofil.
It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. If you are not sure about giving yourself the injection or you have any questions, please ask your doctor or nurse for help.

How do I inject Accofil myself?
You will need to give yourself the injection into the tissue just under the skin. This is known as a subcutaneous injection. You will need to have your injections at about the same time every day.

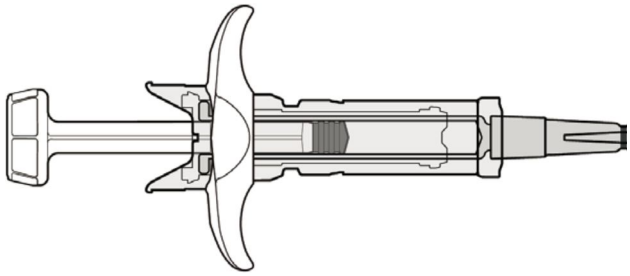
Equipment that you need
To give yourself a subcutaneous injection you will need:
- a pre-filled syringe of Accofil;
- alcohol swab or similar.

What should I do before I give myself a subcutaneous injection of Accofil?
Ensure the needle cover remains on the syringe until just before you are ready to inject.
- Take your Accofil pre-filled syringe out of the refrigerator.
- 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 or if it has been kept outside of the refrigerator for more than 15 days or has otherwise expired.
- Check the appearance of Accofil. It must be a clear and colourless liquid. If there are particles in it, you must not use it.
- For a more comfortable injection, let the pre-filled syringe stand for 30 minutes to reach room temperature or hold the pre-filled syringe gently in your hand for a few minutes. Do not warm Accofil in any other way (for example, do ***not*** warm it in a microwave or in hot water).
- ***Wash your hands thoroughly.***
- Find a comfortable, well-lit place and put everything you need where you can reach them (the Accofil pre-filled syringe and alcohol swab).

How do I prepare my Accofil injection?
Before you inject Accofil you must do the following:
Do not use a pre-filled syringe if it has been dropped on a hard surface.

Step-1: Check the integrity of the system
Ensure the system is intact/ not damaged. Do not use the product if you see any damage (syringe or needle safety guard breakage) or lose components and if the needle safety guard is on safety position before use as shown on picture 9 because this indicate system already operated. In general the product should not be used if it does not conform to the picture 1. If so discard the product in a biohazard (sharps) container

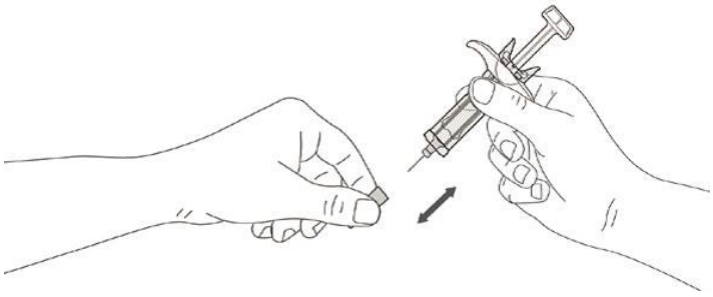
Picture 1



Step 2: Remove the Needle Cap

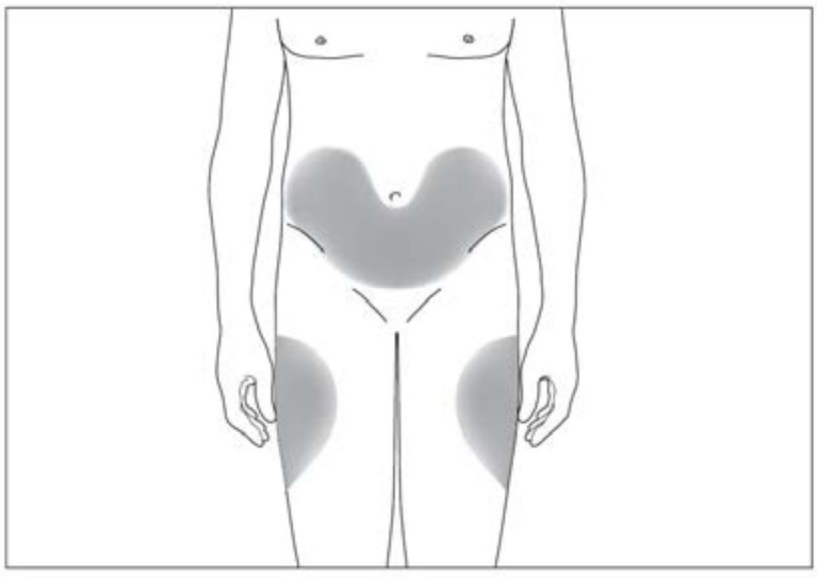
1. Remove the protective cap as shown in picture 2. Hold the body of the needle safety guard in one hand with the needle end pointing away from you and without touching the plunge rod. Pull the needle cap straight off with your other hand. After removal, throw away the needles cap in a biohazard (sharps) container.
2. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
3. The syringe may contain more liquid than you need. Use the scale on the syringe barrel as follows to set the correct dose of Accofil that your doctor prescribed. Eject unnecessary liquid by pushing the plunger up to the number (mL) on the syringe that matches the prescribed dose.
4. Check again to make sure the correct dose of Accofil is in the syringe.
5. You can now use the pre-filled syringe.

Picture 2



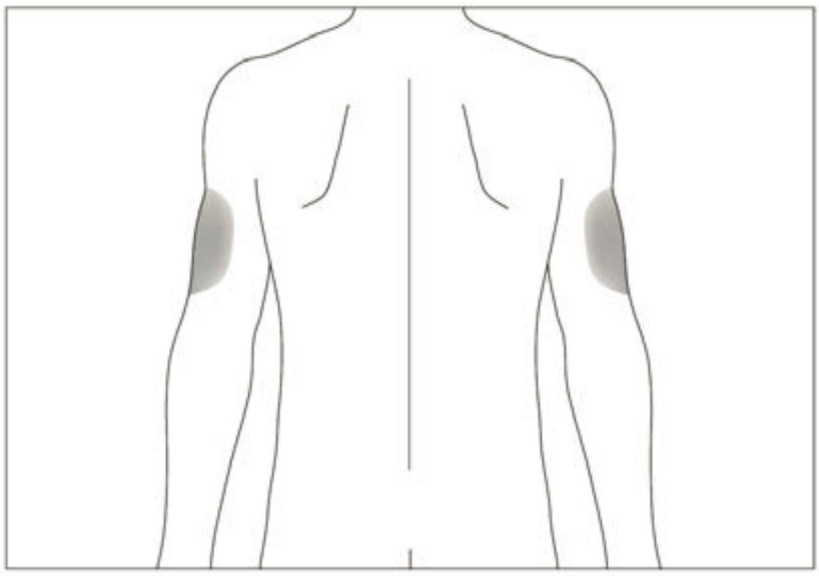
Where should I give my injection?
The most suitable places to inject yourself are:
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).

Picture 3



If someone else is injecting you, they can also use the back of your arms (see picture 4).

Picture 4



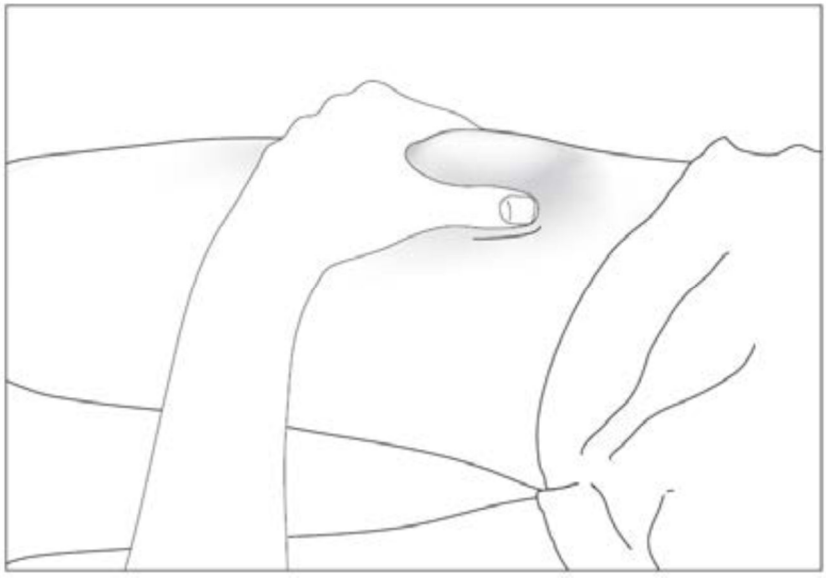
It is better to change the injection site every day to avoid the risk of soreness at any one site.

Step 3 : Insert the Needle

- Lightly pinch the skin at the injection site with one hand;
- With the other hand insert the needle into the injection site without touching the plunger rod head (with 45-90 degree angle) (see picture 6 and 7).

How do I give my injection?
Disinfect the injection site by using an alcohol swab and pinch the skin between your thumb and forefinger, without squeezing it (see picture 5).

Picture 5

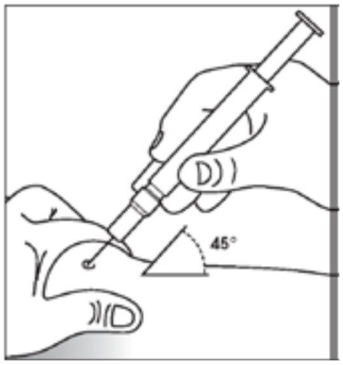


Pre-filled syringe without needle safety guard

a. Put the needle fully into the skin as shown by your nurse or doctor (see picture 6).
b. 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.

c. Always keeping your skin pinched, depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. Do not release the pressure on the plunger!
d. Inject only the dose your doctor has told you.
e. After injecting the liquid, remove the needle while maintaining pressure on the plunger and then let go of your skin.
f. Put the used syringe in the disposal container. Use each syringe only for one injection.

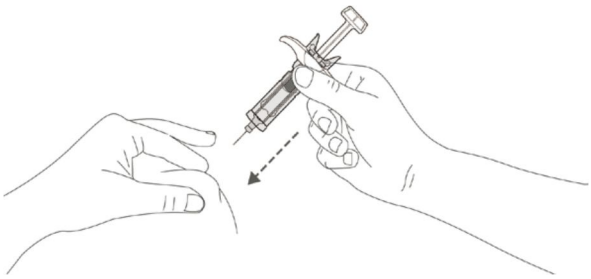
Picture 6



Pre-filled syringe with needle safety guard

1. Put the needle fully into the skin as shown by your nurse or doctor.
2. 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. Inject only the dose your doctor has told you following the instructions below.

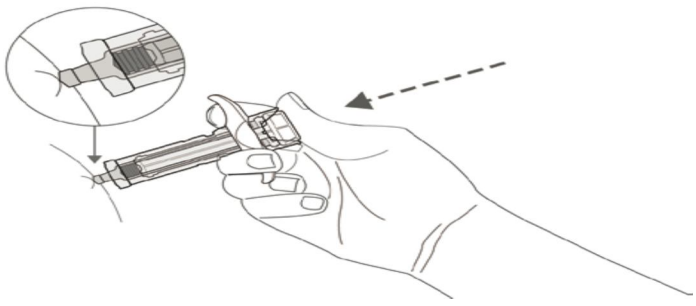
Picture 7



Step-4: Injection

Place the thumb on the plunger rod head. Depress the plunger rod and **push firmly** at the end of the injection to ensure that syringe emptying is completed (see picture 8). Hold the skin securely until the injection is completed

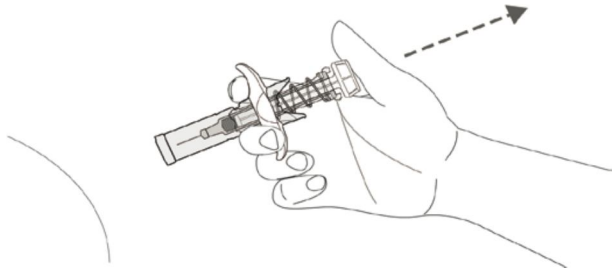
Picture 8



Step-5: Needle Stick Protection

The safety system will activate once the plunger rod is fully depressed:
- Keep the syringe still and slowly lift your thumb from the plunger rod head;
- The plunger rod will move up with your thumb and the spring retracts the needle from the site, into the Needle safety guard (see picture 9).

Picture 9



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

If you use more Accofil 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 Accofil

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 does.

If you have any further questions on the use of this medicine, 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 get left upper belly (abdonimal) 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).
• 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.

A common side effect of Accofil 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 (may affect more than 1 in 10 people):
• 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)
• decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
• low red blood cell count (anaemia)
• fever (pyrexia)
• headache
• diarrhoea

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 (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) (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 macuo-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):
- Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body), 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-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

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in

Appendix V By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Accofil

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 the month.

Store in a refrigerator (2°C - 8°C). Do not freeze.

The syringe can be removed from the refrigerator and left at room temperature (not above 25°C) for a single period, that ends within the labelled expiry date, of up to a maximum of 15 days. At the end of this period, the product should not be put back in the refrigerator and should be disposed of.

Keep the pre-filled syringe in the carton in order to protect from light.

Do not use Accofil if you notice it is cloudy, or there is discoloration or there are particles in it.

Do not put the cover back on used needles, as you may accidentally prick yourself. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Accofil contains

- The active substance is filgrastim. Each pre-filled syringe contains 48 MU (480 micrograms) filgrastim in 0.5 ml, corresponding to 0.96 mg/ml.
- The other ingredients are acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80 and water for injections.

What Accofil looks like and contents of the pack

Accofil is a clear colourless solution for injection or infusion in a pre-filled syringe marked with 1/40 printed markings from 0.1 mL to 1 mL on the syringe barrel, with an injection needle. Each pre-filled syringe contains 0.5 ml of solution.

Accofil is available in packs containing 1, 3, 5, 7 and 10 pre-filled syringes, with or without prefixed needle safety guard and alcohol swabs.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
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This leaflet was last revised in

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

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The following information is intended for medical or healthcare professionals only:

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

Accidental exposure to freezing temperatures for up to 48 hours does not affect the stability of Accofil. If exposure has been greater than 48 hours or frozen more than once then Accofil should NOT be used.

In order to improve traceability of granulocyte-colony stimulating factors, the product name (Accofil) and batch number of the administered product should be clearly recorded in the patient file

Accofil should 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, Accofil may be diluted in 5% glucose. 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, Accofil is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

<u>After dilution:</u>

Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 30 hours at 25 °C ± 2°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 30 hours at 25 °C to ± 2 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Using the pre-filled syringe with a needle safety guard

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger rod and **push firmly** at the end of the injection to ensure that syringe emptying is completed. Hold the skin securely until the injection is completed. Keep the syringe still and slowly lift your thumb from the plunger rod head. The plunger rod will move up with your thumb and the spring retracts the needle from the site, into the Needle safety guard.

Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

Do not use a pre-filled syringe if it has been dropped on a hard surface.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.