

PACKAGE LEAFLET: INFORMATION FOR THE USER

Accofil 30 MU/0.5 ml (0.6 mg/ml) solution for injection or 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.

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 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.

What Accofil is used for

Your doctor has prescribed Accofil for you to help your body make more white blood cells. Your doctor will tell you why you are being treated with Accofil. Accofil is useful in several different conditions which are:

- chemotherapy
- bone marrow transplantation
- severe chronic neutropenia (low number of a type of white blood cells)
- neutropenia (low number of a type of white blood cells) in patients with HIV infection
- peripheral blood stem cell mobilisation (to stimulate stem cells to enter the blood stream to be collected and used in bone marrow transplantation).

2. What you need to know before you use Accofil

Do not use Accofil

- If you are allergic (hypersensitive) 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, 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 that may be (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.
- Experience puffiness in your face or ankles, blood in your urine or brown-coloured 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 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 Accofil, 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

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

You should not receive Accofil in the 24 hours before and the 24 hours after receiving chemotherapy.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Accofil 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.

It is unknown whether filgrastim 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 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 sorbitol and sodium

This medicine contains sorbitol. 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.

This medicine also contains sodium less than 1mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

3. How to use Accofil

Always use Accofil exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The amount of Accofil you need will depend on the condition you are taking Accofil for and on your bodyweight.

Dosage

Accofil and neutropenia (low number of a type of white blood cells) associated with chemotherapy

The usual dose is 0.5 million units (5 micrograms) per kilogram of bodyweight each day. For example, if you weigh 60 kilograms your daily dose will be 30 million units (300 micrograms). Your treatment with Accofil will usually last for about 14 days. In some disease types, however, longer treatment lasting up to about one month may be required.

Accofil and bone marrow transplantation

The usual starting dose is 1 million units (10 micrograms) per kilogram of bodyweight each day given as an infusion. For example, if you weigh 60 kilograms your daily dose will be 60 million units (600 micrograms). 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. Your doctor may then test your blood to see how well the treatment is working and how long it should last.

Accofil and severe chronic neutropenia (low number of a type of white blood cells)

The usual starting dose is between 0.5 million units (5 micrograms) and 1.2 million units (12 micrograms) per kilogram bodyweight each day in a single or divided dose. Your doctor may then test

your blood to see how well your treatment with Accofil is working and to find the dose that is best for you. Long-term treatment with Accofil is required for reduction in neutropenia.

Accofil and neutropenia (low number of a type of white blood cells) in patients with HIV infection

The usual starting dose is between 0.1 million units (1 micrograms) and 0.4 million units (4 micrograms) per kilogram bodyweight each day. Your doctor may test your blood at regular intervals to see how well the Accofil treatment is working. Once the number of white cells in your blood has returned to normal it may be possible to reduce the dose frequency to less than once per day. Long term treatment with Accofil may be required to maintain a normal number of white cells in your blood.

Accofil and peripheral blood stem cell transplantation (stem cells collected from the blood to use in bone marrow transplantation)

If you are donating stem cells for yourself, the usual dose is 0.5 million units (5 micrograms) to 1 million units (10 micrograms) per kilogram bodyweight each day. Accofil treatment will last for up to 2 weeks. Your doctor will monitor your blood to determine the best time to collect the stem cells. If you are acting as a stem cell donor for another person, the usual dose is 1 million units (10 micrograms) per kilogram bodyweight each day. Accofil treatment will last for 4 to 5 days. Your doctor will perform regular blood tests to determine the best time to collect the stem cells.

How Accofil is given

This medicine is given by injection, either 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 give yourself the injections. Your doctor or nurse will give you instructions on how to do this (see information below on instructions for injecting Accofil). Do not attempt to self-administer without this training. Some of the information you require is given at the end of this leaflet, but proper treatment of your disease requires close and constant co-operation with your doctor.

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.

- d. 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).
- e. **Wash your hands thoroughly.**
- f. 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?

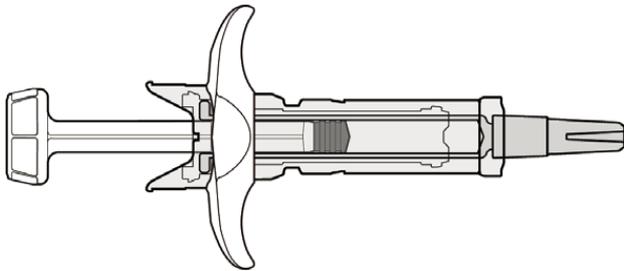
Before you inject Accofil you must do the following:

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

Step-1 : Check the integrity of the system

1. 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 indicates the system is 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.

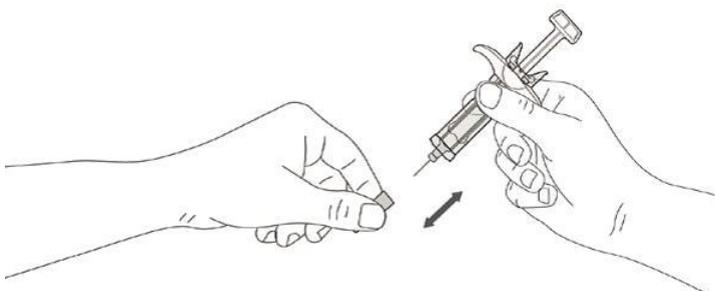
Picture 1



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 plunger rod. Pull the needle cap straight off with your other hand. After removal, throw away the needle 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

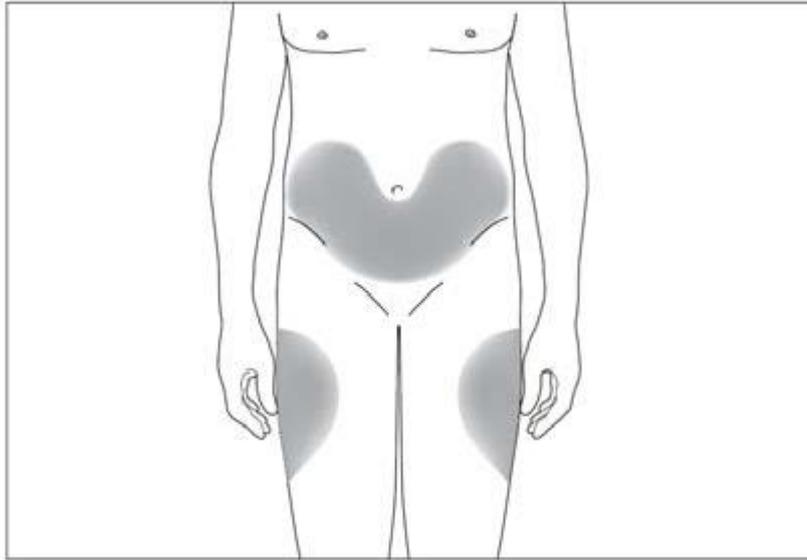


Where should I give my injection?

The most suitable places to inject yourself are:

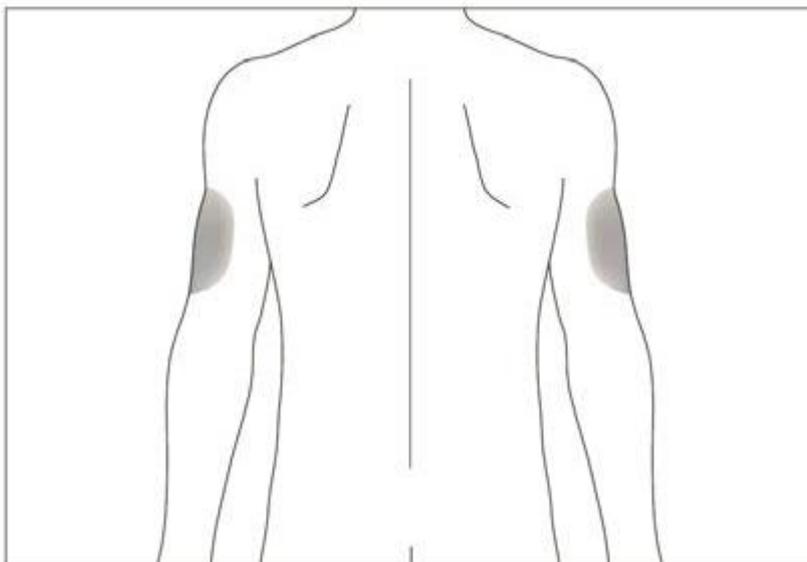
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).

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.

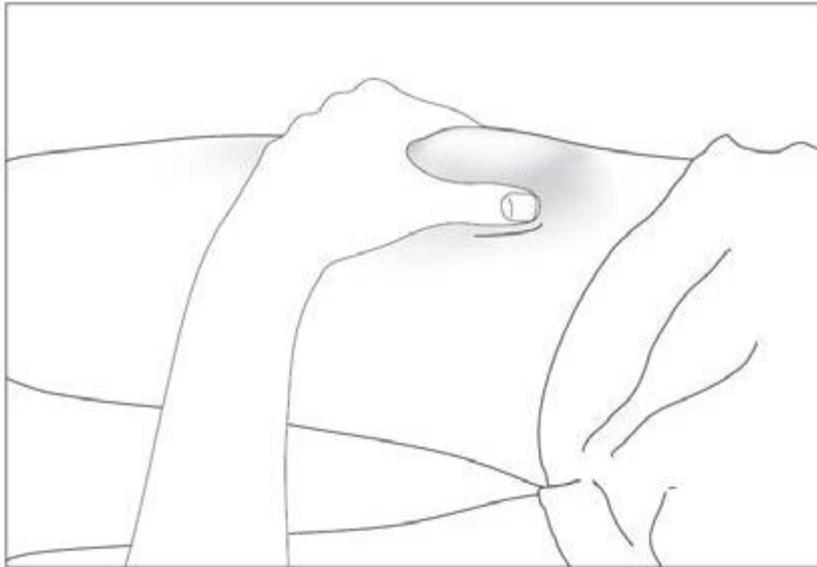
Step 3 : Insert the Needle

- 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?

- a. Disinfect the injection site by using an alcohol swab and pinch the skin between your thumb and forefinger, without squeezing it (see picture 5).

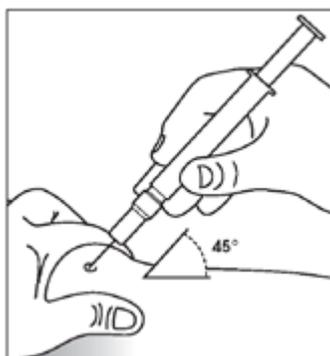
Picture 5



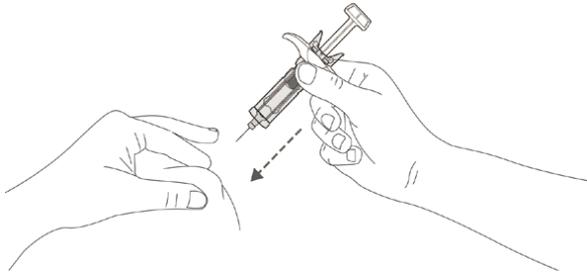
Pre-filled syringe without needle safety guard

- b. Put the needle fully into the skin as shown by your nurse or doctor (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. 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!
e. Inject only the dose your doctor has told you.
f. After injecting the liquid, remove the needle while maintaining pressure on the plunger and then let go of your skin.
g. Put the used syringe in the disposal container. Use each syringe only for one injection.

Picture 6



Picture 7



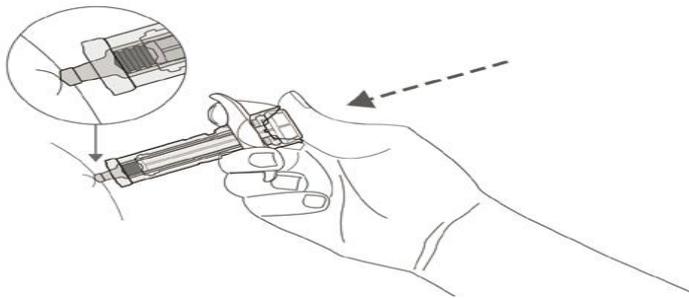
Pre-filled syringe with needle safety guard

- Put the needle fully into the skin as shown by your nurse or doctor (see picture 7).
 - 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.

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

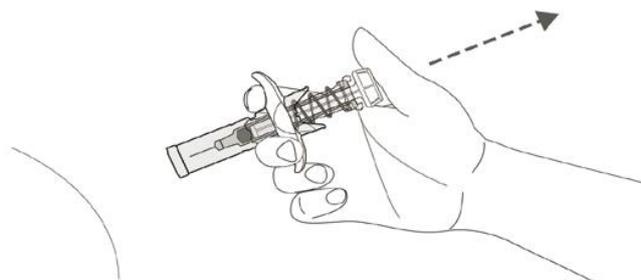


Step-5: Needle Stick Protection

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

If you use more Accofil than you should, contact your doctor or pharmacist as soon as possible.

If you forget to use Accofil

Do not take a double dose to make up for a forgotten injection. Contact your doctor to discuss when you should inject the next dose.

If you stop using Accofil

Your doctor will tell you when to stop using Accofil. It is quite normal to have a number of courses of treatment with Accofil.

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

4. Possible side effects

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

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). Hypersensitivity is common in patients with cancer;
- if you experience a cough, fever and difficulty breathing (dyspnoea) as this can be a sign of Acute Respiratory Distress Syndrome (ARDS). ARDS is uncommon in patients with cancer;
- if you get left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of your shoulder since this may relate to 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 a 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 an uncommon condition (may affect up to 1 in 100 people) called Capillary Leak Syndrome which causes the 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 experience kidney injury (glomerulonephritis). Kidney injury has been seen in patients who received Accofil. 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

A very frequent 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 and soles of your feet and ulcer and sores in your mouth, gut, liver, skin, or your eyes, lungs, vagina and joints. Very commonly seen in normal stem cells donors is increase in white blood cells (leukocytosis) and decrease of platelets which reduces the ability of blood to clot (thrombocytopenia), these will be monitored by your doctor.

Very common side effects (seen in more than 1 in 10 people who take Accofil):

- 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 (seen in more than 1 in 100 people taking Accofil):

- 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 (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 (seen in more than 1 in 1000 people taking Accofil):

- 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 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 (seen in more than 1 in 10,000 people taking Accofil):

- 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

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Accofil

Keep 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 30 MU (300 micrograms) filgrastim in 0.5 ml, corresponding to 0.6 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.

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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.

After dilution

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 ± 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 slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

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.