ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Accofil 30 MU/0.5 ml solution for injection/infusion in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 30 million units (MU)/300 micrograms (µg) of filgrastim in 0.5 ml (0.6 mg/ml) solution for injection or infusion.

Filgrastim is a recombinant methionyl human granulocyte-colony stimulating factor produced in *Escherichia coli* (BL21) by recombinant DNA technology.

Excipient with known effect:

Each ml of solution contains 50 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe

Concentrate for solution for infusion in pre-filled syringe

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Accofil is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of Accofil are similar in adults and children receiving cytotoxic chemotherapy.

Accofil is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs).

In patients, children or adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, long term administration of Accofil is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Accofil is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

4.2 Posology and method of administration

Accofil therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration

with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Posology
Established cytotoxic chemotherapy

The recommended dose of filgrastim is 0.5 MU (5 µg)/kg/day. The first dose of Accofil should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 µg/m^2/day (4.0 to 8.4 µg/kg/day) was used.

Daily dosing with filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, lymphomas, and lymphoid leukaemia, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days. Following induction and consolidation treatment for acute myeloid leukaemia the duration of treatment may be substantially longer (up to 38 days) depending on the type, dose and schedule of cytotoxic chemotherapy used.

In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1-2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of filgrastim therapy, prior to the time of the expected neutrophil nadir, is not recommended.

In patients treated with myeloablative therapy followed by bone marrow transplantation
The recommended starting dose of filgrastim is 1.0 MU (10 µg)/kg/day. The first dose of filgrastim should be administered at least 24 hours following cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

Once the neutrophil nadir has been passed, the daily dose of filgrastim should be titrated against the neutrophil response as follows:

Neutrophil count	**Filgrastim dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 0.5 MU (5 µg)/kg/day
Then, if ANC remains > 1.0 x 10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0 x 10^9/L during the treatment period the dose of filgrastim should be re-escalated according to the above steps	

ANC = absolute neutrophil count

For mobilisation of PBPC in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation
The recommended dose of Accofil for PBPC mobilisation when used alone is 1.0 MU (10 µg)/kg/day for 5-7 consecutive days. Timing of leukapheresis: 1 or 2 leukapheresis on days 5 and 6 are often sufficient. In other circumstances, additional leukapheresis may be necessary. Filgrastim dosing should be maintained until the last leukapheresis.

The recommended dose of filgrastim for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MU (5 µg)/kg/day from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from < 0.5 x 10^9/L to > 5.0 x 10^9/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis are recommended.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation
For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU (10 µg)/kg/day for 4 to 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4 x 10^6 $CD34^+$ cells/kg recipient bodyweight.

In patients with severe chronic neutropenia (SCN)
Congenital neutropenia
The recommended starting dose is 1.2 MU (12 µg)/kg/day as a single dose or in divided doses.

Idiopathic or cyclic neutropenia
The recommended starting dose is 0.5 MU (5 µg)/kg/day as a single dose or in divided doses.

Dose adjustments
Filgrastim should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than 1.5 x 10^9/L. When the response has been obtained, the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently, the dose may be individually adjusted every 1 to 2 weeks to maintain the average neutrophil count between 1.5 x 10^9/L and 10 x 10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97% of patients who responded had a complete response at doses of ≤ 24 µg/kg/day. The long-term safety of administration of filgrastim at doses above 24 µg/kg/day in patients with SCN has not been established.

In patients with HIV infection

For reversal of neutropenia
The recommended starting dose of filgrastim is 0.1 MU (1 µg)/kg/day, with titration up to a maximum of 0.4 MU (4 µg)/kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0 x 10^9/L). In clinical studies, more than 90% of patients responded at these doses, achieving reversal of neutropenia in a median of 2 days.

In a small number of patients (< 10%), doses up to 1.0 MU (10 µg)/kg/day were required to achieve reversal of neutropenia.

For maintenance of normal neutrophil counts
When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU (300 µg)/day is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2.0 x 10^9/L. In clinical studies, dosing with 30 MU (300 µg)/day on 1 - 7 days per week was required to maintain the ANC > 2.0 x 10^9/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC > 2.0 x 10^9/L.

Special population
Elderly
Clinical trials with filgrastim have included a small number of elderly patients but special studies have not been performed in this group and therefore specific dosage recommendations cannot be made.

Patients with renal impairment
Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.

Paediatric use in the SCN and cancer settings
Sixty-five percent of the patients studied in the SCN trial programme were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for SCN.

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are

similar in both adults and children receiving cytotoxic chemotherapy.

The dosage recommendations in paediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy.

Method of administration

Established cytotoxic chemotherapy
Filgrastim may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minute (see section 6.6). The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance.

In patients treated with myeloablative therapy followed by bone marrow transplantation
Filgrastim may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion.
Filgrastim should be diluted in 20 mL of 5% glucose solution (see section 6.6).

For the mobilisation of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation
Filgrastim for PBPC mobilisation when used alone:
Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions filgrastim should be diluted in 20ml of 5% glucose solution (see section 6.6).

Filgrastim for PBPC mobilisation after myelosuppressive chemotherapy
Filgrastim should be given by subcutaneous injection.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation
Filgrastim should be given by subcutaneous injection.

In patients with severe chronic neutropenia (SCN)
Congenital, idiopathic or cyclic neutropenia, filgrastim should be given by subcutaneous injection.

In patients with HIV infection
Reversal of neutropenia and maintaining of normal neutrophil counts: filgrastim should be given by subcutaneous injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Special warning and precautions across indications

Hypersensitivity
Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with filgrastim. Permanently discontinue filgrastim in patients with clinically significant hypersensitivity. Do not administer filgrastim to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Pulmonary adverse effects
Pulmonary adverse effects, in particular interstitial lung disease, have been reported after G-CSF administration. Patients with a recent history of lung infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given.

Glomerulonephritis
Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Capillary leak syndrome
Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after granulocyte-colony stimulating factor administration, and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see section 4.8).

Splenomegaly and splenic rupture
Generally asymptomatic cases of splenomegaly and cases of splenic rupture have been reported in patients and normal donors following administration of filgrastim. Some cases of splenic rupture were fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal or shoulder tip pain. Dose reductions of Filgrastim have been noted to slow or stop the progression of splenic enlargement in patients with severe chronic neutropenia, and in 3% of patients a splenectomy was required.

Malignant cell growth
Granulocyte-colony stimulating factor can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

Myelodysplastic syndrome or Chronic myeloid leukaemia
The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia have not been established. Filgrastim is not indicated for use in these conditions. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

Acute myeloid leukaemia
In view of limited safety and efficacy data in patients with secondary AML, filgrastim should be administered with caution. The safety and efficacy of filgrastim administration in *de novo* AML patients aged < 55 years with good cytogenetics [t (8; 21), t (15; 17), and inv (16)] have not been established.

Thrombocytopenia
Thrombocytopenia has been reported in patients receiving filgrastim. Platelet counts should be monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to temporary discontinuation or dose reduction of filgrastim in patients with severe chronic neutropenia who develop thrombocytopenia (platelet count < 100×10^9/L).

Leukocytosis
White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5% of cancer patients receiving filgrastim at doses above 0.3 MU/kg/day (3 µg/kg/day). No undesirable effects directly attributable to this degree of leukocytosis have been reported. However, in view of the potential risks associated with severe leukocytosis, a white blood cell count should be performed at

regular intervals during filgrastim therapy. If leukocyte counts exceed 50 x 10^9/L after the expected nadir, filgrastim should be discontinued immediately. When administered for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against filgrastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

Aortitis
Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also section 4.8.

Special warnings and precautions associated with co-morbidities

Special precautions in sickle cell trait and sickle cell disease
Sickle cell crises, in some cases fatal, have been reported with the use of filgrastim in patients with sickle cell trait or sickle cell disease. Physicians should use caution when prescribing filgrastim in patients with sickle cell trait or sickle cell disease.

Osteoporosis
Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with filgrastim for more than 6 months.

Special precautions in cancer patients

Filgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Risks associated with increased doses of chemotherapy
Special caution should be used when treating patients with high-dose chemotherapy because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the prescribing information of the specific chemotherapy agents used).

Effect of chemotherapy on erythrocytes and thrombocytes
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Because of the potential of receiving higher doses of chemotherapy (e.g. full doses on the prescribed schedule) the patient may be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

The use of filgrastim-mobilised PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Myelodysplastic syndrome and acute myeloid leukaemia in breast and lung cancer patients
In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim, an alternative G-CSF medicine, in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association between filgrastim and MDS/AML has not been observed. Nonetheless, patients with breast cancer and patients with lung cancer should be monitored for signs and symptoms of MDS/AML.

Other special precautions
The effects of filgrastim in patients with substantially reduced myeloid progenitors have not been studied. Filgrastim acts primarily on neutrophil precursors to exert its effect in elevating neutrophil counts. Therefore, in patients with reduced precursors, neutrophil response may be diminished (such as those treated with extensive radiotherapy or chemotherapy, or those with bone marrow infiltration by tumour).

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high-dose chemotherapy followed by transplantation.

There have been reports of graft versus host disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 4.8 and 5.1).

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient abnormal bone scans. This should be considered when interpreting bone-imaging results.

Special precautions in patients undergoing PBPC mobilisation

Mobilisation
There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of $CD34^+$ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an optimum method. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Prior exposure to cytotoxic agents
Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield ($\geq 2.0 \times 10^6$ $CD34^+$ cells/kg) or acceleration of platelet recovery to the same degree.

Some cytotoxic agents exhibit particular toxicities to the haematopoietic progenitor pool and may adversely affect progenitor mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilisation, may reduce progenitor yield. However, the administration of melphalan, carboplatin or carmustine (BCNU) together with filgrastim has been shown to be effective for progenitor mobilisation. When a PBPC transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment, not requiring progenitor support should be considered.

Assessment of progenitor cell yields
In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of $CD34^+$ cell numbers vary depending on the precise methodology used and recommendations of numbers based on studies in other laboratories need to be interpreted with caution.

Statistical analysis of the relationship between the number of $CD34^+$ cells re-infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship.

The recommendation of a minimum yields of $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg is based on published experience resulting in adequate haematologic reconstitution. Yields in excess of this appear to correlate with more rapid recovery, those below with slower recovery.

Special precautions in normal donors undergoing PBPC mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to haematological values and infectious diseases.

The safety and efficacy of filgrastim has not been assessed in normal donors less than 16 years or greater than 60 years.

Transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets < 50 x 10^9/L were reported and attributed to the leukapheresis procedure.

If more than one leukapheresis is required, particular attention should be paid to donors with platelets < 100 x 10^9/L prior to leukapheresis; in general apheresis should not be performed if platelets < 75 x 10^9/L.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis. Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.

Special precautions in recipients of allogeneic PBPCs mobilised with filgrastim

Current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic GvHD when compared with bone marrow transplantation.

Special precautions in SCN patients

Filgrastim should not be administered to patients with severe congenital neutropenia who develop leukaemia or have evidence of leukaemic evolution.

Blood cell counts
Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.

Transformation to leukaemia or myelodysplastic syndrome
Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia and myeloid leukaemia. Complete blood cell counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukaemias are natural complications of the disease and are of uncertain relation to filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. It is currently unclear whether long-term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions
Causes of transient neutropenia such as viral infections should be excluded.

Haematuria was common and proteinuria occurred in a small number of patients. Regular urinalysis should be performed to monitor these events.

The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established.

Special precautions in patients with HIV infection

Blood cell counts
Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 µg)/day of filgrastim, there can be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples are taken for ANC measurement immediately prior to any scheduled dosing with filgrastim.

Risk associated with increased doses of myelosuppressive medicinal products
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medicinal products. As a result of the potential to receive higher doses or a greater number of these medicinal products with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

Infections and malignancies causing myelosuppression
Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infections or malignancy, consider appropriate therapy for treatment of the underlying condition in addition to administration of filgrastim for treatment of neutropenia. The effects of filgrastim on neutropenia due to bone marrow-infiltrating infection or malignancy have not been well established.

All patients
Accofil contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.
Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Accofil contains less than 1mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

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

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of filgrastim given on the same day as myelosuppressive cytotoxic chemotherapy have not been definitively established. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of filgrastim is not recommended in the period from 24 hours before to 24 hours after chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with filgrastim and 5-Fluorouracil indicates that the severity

of neutropenia may be exacerbated.

Possible interactions with other haematopoietic growth factors and cytokines have not yet been investigated in clinical trials.

Since lithium promotes the release of neutrophils, lithium is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3). There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.

Filgrastim is not recommended during pregnancy.

Breast-feeding

It is unknown whether filgrastim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from filgrastim therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Filgrastim did not affect reproductive performance or fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Accofil may have a minor influence on the ability to drive and use machines.

Dizziness may occur following the administration of Accofil (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse reactions that may occur during Filgrastim treatment include: anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, severe splenomegaly/splenic rupture, transformation to myelodysplastic syndrome or leukaemia in SCN patients, GvHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant and sickle cell crisis in patients with sickle cell disease.

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea. In clinical trials in cancer patients musculoskeletal pain was mild or moderate in 10%, and severe in 3% of patients.

b. Tabulated summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping undesirable effects are presented in order of decreasing

seriousness.

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia Anaemia[e]	Splenomegaly[a] Haemoglobin decreased[e]	Leukocytosis[a]	Splenic rupture[a] Sickle cell anaemia with crisis Extramedullary haematopoiesis
Immune system disorders			Hypersensitivity Drug hypersensitivity[a] Graft versus host disease[b]	Anaphylactic reaction
Metabolism and nutrition disorders		Decreased appetite[e] Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout[a] (Chondrocalcinosis Pyrophosphate) Fluid volume disturbances
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache[a]	Dizziness, Hypoaesthesia, Paraesthesia		
Vascular disorders		Hypotension Hypertension	Veno-occlusive disease[d]	Capillary leak syndrome[a], Aortitis
Respiratory, thoracic and mediastinal disorders		Haemoptysis Dyspnoea Cough[a] Oropharyngeal pain[a,e] Epistaxis	Acute respiratory distress syndrome[a] Respiratory failure[a]	

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
			Pulmonary oedema[a] Interstitial lung disease[a] Lung infiltration[a] Pulmonary haemorrhage Hypoxia	
Gastrointestinal disorders	Diarrhoea[a,e] Vomiting[a,e] Nausea[a]	Constipation[e] Oral pain		
Hepatobiliary disorders		Blood alkaline phosphatase increased Hepatomegaly	Gamma-glutamyl transferase increased Aspartate aminotransferase increased	
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Rash maculopapular	Sweets syndrome (acute febrile neutrophilic dermatosis) Cutaneous vasculitis[a]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[c]	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Urine abnormality Glomerulonephritis
General disorders and administration site conditions	Fatigue[a] Mucosal inflammation[a] Pyrexia	Chest pain[a] Asthenia[a] Pain[a] Malaise[e] Oedema peripheral[e]	Injection site reaction	
Injury, poisoning and procedural complications		Transfusion reaction[e]		

[a] See section c (Description of selected adverse reactions)
[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section c)
[c] Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain
[d] Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC mobilisation
[e] Adverse events with higher incidence in Filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy

c. Description of selected adverse reactions

GvHD
There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see sections 4.4 and 5.1).

Capillary leak syndrome
Cases of capillary leak syndrome have been reported with granulocyte-colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

Sweets syndrome
Cases of Sweets syndrome (acute febrile neutrophilic dermatosis) have been reported in patients treated with filgrastim.

Pulmonary adverse events
In clinical studies and the post-marketing setting pulmonary adverse effects including interstitial lung disease, pulmonary oedema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4)

Splenomegaly and Splenic rupture
Cases of splenomegaly and splenic rupture have been reported following administration of filgrastim. Some cases of splenic rupture were fatal (see section 4.4).

Hypersensitivity
Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post-marketing experience. Overall, reports were more common after IV administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Cutaneous vasculitis
Cutaneous vasculitis has been reported in patients treated with Filgrastim. The mechanism of vasculitis in patients receiving Filgrastim is unknown. During long term use cutaneous vasculitis has been reported in 2% of SCN patients.

Pseudogout (chondrocalcinosis pyrophosphate)
Pseudogout (chondrocalcinosis pyrophosphate) has been reported in cancer patients treated with filgrastim.

Leukocytosis
Leukocytosis (WBC > 50 x 10^9/L) was observed in 41% of normal donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35% of donors (see section 4.4).

d. Paediatric population

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy suggesting no age-related differences in the pharmacokinetics of filgrastim. The only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

There is insufficient data to further evaluate filgrastim use in paediatric subjects.

e. Other special populations

Geriatric use
No overall differences in safety or effectiveness were observed between subjects over 65 years of age compared to younger adult (>18 years of age) subjects receiving cytotoxic chemotherapy and clinical experience has not identified differences in the responses between elderly and younger adult patients. There is insufficient data to evaluate Accofil use in geriatric subjects for other approved Accofil indications.

Paediatric SCN patients
Cases of decreased bone density and osteoporosis have been reported in paediatric patients with severe chronic neutropenia receiving chronic treatment with filgrastim.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The effects of Accofil overdosage have not been established. Discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factors, ATC code: L03AA02
Accofil is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu
Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Accofil containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes. In some SCN patients, filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.

Use of filgrastim in patients undergoing cytotoxic chemotherapy leads to significant reductions in the incidence, severity and duration of neutropenia and febrile neutropenia. Treatment with filgrastim significantly reduces the duration of febrile neutropenia, antibiotic use and hospitalisation after induction chemotherapy for acute myelogenous leukaemia or myeloablative therapy followed by bone

marrow transplantation. The incidence of fever and documented infections were not reduced in either setting. The duration of fever was not reduced in patients undergoing myeloablative therapy followed by bone marrow transplantation.

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into the peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

Recipients of allogeneic PBPCs mobilised with filgrastim experienced significantly more rapid haematological recovery, leading to a significant decrease in time to unsupported platelet recovery when compared with allogeneic bone marrow transplantation.

One retrospective European study evaluating the use of G-CSF after allogeneic bone marrow transplantation in patients with acute leukaemias suggested an increase in the risk of GvHD, treatment related mortality (TRM) and mortality when G-CSF was administered. In a separate retrospective international study in patients with acute and chronic myelogenous leukaemias, no effect on the risk of GvHD, TRM and mortality was seen. A meta-analysis of allogeneic transplant studies, including the results of nine prospective randomized trials, 8 retrospective studies and 1 case-controlled study, did not detect an effect on the risks of acute GvHD, chronic GvHD or early treatment-related mortality.

Relative risk (95% CI) of GvHD and TRM following treatment with G-CSF after bone marrow (BM) transplantation					
Publication	**Period of Study**	**N**	**Acute Grade II - IV GvHD**	**Chronic GvHD**	**TRM**
Meta-Analysis (2003)	1986 - 2001[a]	1198	1.08 (0.87, 1.33)	1.02 (0.82, 1.26)	0.70 (0.38, 1.31)
European Retrospective Study (2004)	1992 - 2002[b]	1789	1.33 (1.08, 1.64)	1.29 (1.02, 1.61)	1.73 (1.30, 2.32)
International Retrospective Study (2006)	1995 - 2000[b]	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)

[a] Analysis includes studies involving BM transplant during this period; some studies used GM-CSF

[b] Analysis includes patients receiving BM transplant during this period

Use of filgrastim for the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

In normal donors, a 10 µg/kg/day dose administered subcutaneously for 4 - 5 consecutive days allows a collection of $\geq 4 \times 10^6$ $CD34^+$ cells/kg recipient body weight in the majority of the donors after two leukaphereses.

Use of filgrastim in patients, children or adults, with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in absolute neutrophil counts in peripheral blood and a reduction of infection and related events.

Use of filgrastim in patients with HIV infection maintains normal neutrophil counts to allow scheduled dosing of antiviral and/or other myelosuppressive medication. There is no evidence that patients with HIV infection treated with filgrastim show an increase in HIV replication.

As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/ml for 8 - 16 hours.

Distribution

The volume of distribution in blood is approximately 150 ml/kg.

Elimination

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half-life of filgrastim is approximately 3.5 hours, with a clearance rate of approximately 0.6 ml/min/kg. Continuous infusion with Accofil over a period of up to 28 days, in patients recovering from autologous bone-marrow transplantation, resulted in no evidence of drug accumulation and comparable elimination half-lives.

Linearity

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

5.3 Preclinical safety data

Filgrastim was studied in repeated dose toxicity studies up to 1 year in duration which revealed changes attributable to the expected pharmacological actions including increases in leucocytes , myeloid hyperplasia in bone marrow, extramedullary granulopoiesis and splenic enlargement. These changes all reversed after discontinuation of treatment.
Effects of filgrastim on prenatal development have been studied in rats and rabbits. Intravenous (80 µg/kg/day) administration of filgrastim to rabbits during the period of organogenesis was maternally toxic and increased spontaneous abortion, post-implantation loss, and decreased mean live litter size and foetal weight were observed.
Based on reported data for another filgrastim product similar to Accofil, comparable findings plus increased foetal malformations were observed at 100 µg/kg/day, a maternally toxic dose which corresponded to a systemic exposure of approximately 50-90 times the exposures observed in patients treated with the clinical dose of 5 µg/kg/day. The no observed adverse effect level for embryo-foetal toxicity in this study was 10 µg/kg/day, which corresponded to a systemic exposure of approximately 3-5 times the exposures observed in patients treated with the clinical dose.
In pregnant rats, no maternal or foetal toxicity was observed at doses up to 575 µg/kg/day. Offspring of rats administered filgrastim during the peri-natal and lactation periods, exhibited a delay in external differentiation and growth retardation (≥20 µg/kg/day) and slightly reduced survival rate (100 µg/kg/day).
Filgrastim had no observed effect on the fertility of male or female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid glacial
Sodium hydroxide
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

Accofil must not be diluted with sodium chloride solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

This medicinal product must not be mixed with other products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

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

Within its shelf-life and for the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 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 syringe in the outer carton in order to protect from light.

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.

6.5 Nature and contents of container

Type I glass pre-filled syringe with a permanently attached stainless steel needle in the tip and 1/40 printed markings for graduations from 0.1 mL to 1 mL on the barrel. The needle cover of the pre-filled syringe contains dry natural rubber (see section 4.4). Each pre-filled syringe contains 0.5 ml solution.

Each pack contains one, three, five, seven or ten pre-filled syringes, with or without a needle safety guard, and alcohol swab(s). The packs without blister are for syringes without needle safety guard. The blister packs are for individual syringes with prefixed needle safety guard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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. Do not shake.

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.

Accofil contains no preservative. In view of the possible risk of microbial contamination, Accofil pre-filled syringes are for single use only.

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

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.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/001
EU/1/14/946/002
EU/1/14/946/005
EU/1/14/946/006
EU/1/14/946/007
EU/1/14/946/008
EU/1/14/946/009
EU/1/14/946/010
EU/1/14/946/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 18.09.2014
Date of latest renewal: 12th June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Accofil 48 MU/0.5 ml solution for injection/infusion in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 48 million units (MU)/480 micrograms (µg) of filgrastim in 0.5 ml (0.96 mg/ml) solution for injection or infusion.

Filgrastim is a recombinant methionyl human granulocyte-colony stimulating factor produced in *Escherichia coli* (BL21) by recombinant DNA technology.

Excipient with known effect:

Each ml of solution contains 50 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe

Concentrate for solution for infusion in pre-filled syringe

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Accofil is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

The safety and efficacy of Accofil are similar in adults and children receiving cytotoxic chemotherapy.

Accofil is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs).

In patients, children or adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, long term administration of Accofil is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Accofil is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

4.2 Posology and method of administration

Accofil therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration

with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Posology

Established cytotoxic chemotherapy

The recommended dose of filgrastim is 0.5 MU (5 µg)/kg/day. The first dose of Accofil should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 µg/m^2/day (4.0 to 8.4 µg/kg/day) was used.

Daily dosing with filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, lymphomas, and lymphoid leukaemia, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days. Following induction and consolidation treatment for acute myeloid leukaemia the duration of treatment may be substantially longer (up to 38 days) depending on the type, dose and schedule of cytotoxic chemotherapy used.

In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1-2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of filgrastim therapy, prior to the time of the expected neutrophil nadir, is not recommended.

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of filgrastim is 1.0 MU (10 µg)/kg/day. The first dose of filgrastim should be administered at least 24 hours following cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

Once the neutrophil nadir has been passed, the daily dose of filgrastim should be titrated against the neutrophil response as follows:

Neutrophil count	**Filgrastim dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 0.5 MU (5 µg)/kg/day
Then, if ANC remains > 1.0 x 10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0 x 10^9/L during the treatment period, the dose of filgrastim should be re-escalated according to the above steps	

ANC = absolute neutrophil count

For mobilisation of PBPC in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU (10 µg)/kg/day for 5-7 consecutive days. Timing of leukapheresis: 1 or 2 leukapheresis on days 5 and 6 which is often sufficient. In other circumstances, additional leukapheresis may be necessary. Filgrastim dosing should be maintained until the last leukapheresis.

The recommended dose of filgrastim for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MU (5 µg)/kg/day from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from < 0.5 x 10^9/L to > 5.0 x 10^9/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis are recommended.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU (10 µg)/kg/day for 4 to 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4 x 10^6 $CD34^+$ cells/kg recipient bodyweight.

In patients with severe chronic neutropenia (SCN)

Congenital neutropenia
The recommended starting dose is 1.2 MU (12 µg)/kg/day as a single dose or in divided doses.

Idiopathic or cyclic neutropenia
The recommended starting dose is 0.5 MU (5 µg)/kg/day as a single dose or in divided doses.

Dose adjustments
Filgrastim should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than 1.5 x 10^9/L. When the response has been obtained, the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently, the dose may be individually adjusted every 1 to 2 weeks to maintain the average neutrophil count between 1.5 x 10^9/L and 10 x 10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trial, 97% of patients who responded had a complete response at doses of ≤ 24 µg/kg/day. The long-term safety of administration of filgrastim at doses above 24 µg/kg/day in patients with SCN has not been established.

In patients with HIV infection
For reversal of neutropenia
The recommended starting dose of filgrastim is 0.1 MU (1 µg)/kg/day given daily with titration up to a maximum of 0.4 MU (4 µg)/kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0 x 10^9/L). In clinical studies, more than 90% of patients responded at these doses, achieving reversal of neutropenia in a median of 2 days.

In a small number of patients (< 10%), doses up to 1.0 MU (10 µg) /kg/day were required to achieve reversal of neutropenia.

For maintenance of normal neutrophil counts
When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU (300 µg)/day is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2.0 x 10^9/L. In clinical studies, dosing with 30 MU (300 µg)/day on 1 - 7 days per week was required to maintain the ANC > 2.0 x 10^9/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC > 2.0 x 10^9/L.

Special populations
Elderly
Clinical trials with filgrastim have included a small number of elderly patients but special studies have not been performed in this group and therefore specific dosage recommendations cannot be made.

Patients with renal impairment
Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.

Paediatric use in the SCN and cancer settings
Sixty-five percent of the patients studied in the SCN trial programme were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for SCN.

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy.

The dosage recommendations in paediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy.

Method of administration

Established cytotoxic chemotherapy
Filgrastim may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minute (see section 6.6). The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance.

In patients treated with myeloablative therapy followed by bone marrow transplantation
Filgrastim may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 mL of 5% glucose solution (see section 6.6).

For the mobilisation of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation
Filgrastim for PBPC mobilisation when used alone:
Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions filgrastim should be diluted in 20ml of 5% glucose solution (see section 6.6).

Filgrastim for PBPC mobilisation after myelosuppressive chemotherapy
Filgrastim should be given by subcutaneous injection.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation
Filgrastim should be given by subcutaneous injection.

In patients with severe chronic neutropenia (SCN)
Congenital, idiopathic or cyclic neutropenia, filgrastim should be given by subcutaneous injection.

In patients with HIV infection
Reversal of neutropenia and maintaining of normal neutrophil counts: filgrastim should be given by subcutaneous injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Special warning and precautions across indications

Hypersensitivity
Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with filgrastim. Permanently discontinue filgrastim in patients with

clinically significant hypersensitivity. Do not administer filgrastim to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Pulmonary adverse effects
Pulmonary adverse effects, in particular interstitial lung disease, have been reported after G-CSF administration. Patients with a recent history of lung infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given.

Glomerulonephritis
Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Capillary leak syndrome
Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after granulocyte-colony stimulating factor administration, and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see section 4.8).

Splenomegaly and splenic rupture
Generally asymptomatic cases of splenomegaly and cases of splenic rupture have been reported in patients and normal donors following administration of filgrastim. Some cases of splenic rupture were fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal or shoulder tip pain. Dose reductions of Filgrastim have been noted to slow or stop the progression of splenic enlargement in patients with severe chronic neutropenia, and in 3% of patients a splenectomy was required.

Malignant cell growth
Granulocyte-colony stimulating factor can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

Myelodysplastic syndrome or Chronic myeloid leukaemia
The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia have not been established. Filgrastim is not indicated for use in these conditions. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

Acute myeloid leukaemia
In view of limited safety and efficacy data in patients with secondary AML, filgrastim should be administered with caution. The safety and efficacy of filgrastim administration in *de novo* AML patients aged < 55 years with good cytogenetics [t (8; 21), t (15; 17), and inv (16)] have not been established.

Thrombocytopenia
Thrombocytopenia has been reported in patients receiving filgrastim. Platelet counts should be monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to temporary discontinuation or dose reduction of filgrastim in patients with severe chronic neutropenia who develop thrombocytopenia (platelet count < 100×10^9/L).

Leukocytosis
White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5% of cancer patients receiving filgrastim at doses above 0.3 MU/kg/day (3 µg/kg/day). No undesirable effects

directly attributable to this degree of leukocytosis have been reported. However, in view of the potential risks associated with severe leukocytosis, a white blood cell count should be performed at regular intervals during filgrastim therapy. If leukocyte counts exceed 50 x 10^9/L after the expected nadir, filgrastim should be discontinued immediately. When administered for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against filgrastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

Aortitis
Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also section 4.8.

Special warnings and precautions associated with co-morbidities

Special precautions in sickle cell trait and sickle cell disease
Sickle cell crises, in some cases fatal, have been reported with the use of filgrastim in patients with sickle cell trait or sickle cell disease. Physicians should use caution when prescribing filgrastim in patients with sickle cell trait or sickle cell disease.

Osteoporosis
Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with filgrastim for more than 6 months.

Special precautions in cancer patients

Filgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Risks associated with increased doses of chemotherapy
Special caution should be used when treating patients with high-dose chemotherapy because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the prescribing information of the specific chemotherapy agents used).

Effect of chemotherapy on erythrocytes and thrombocytes
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Because of the potential of receiving higher doses of chemotherapy (e.g. full doses on the prescribed schedule) the patient may be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

The use of filgrastim-mobilised PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Myelodysplastic syndrome and acute myeloid leukaemia in breast and lung cancer patients
In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim, an alternative G-CSF medicine, in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association between filgrastim and MDS/AML has not been observed. Nonetheless, patients with breast cancer and patients with lung cancer should be monitored for signs and symptoms of

MDS/AML.

Other special precautions
The effects of filgrastim in patients with substantially reduced myeloid progenitors have not been studied. Filgrastim acts primarily on neutrophil precursors to exert its effect in elevating neutrophil counts. Therefore, in patients with reduced precursors, neutrophil response may be diminished (such as those treated with extensive radiotherapy or chemotherapy, or those with bone marrow infiltration by tumour).

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high-dose chemotherapy followed by transplantation. There have been reports of graft versus host disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 4.8 and 5.1).

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient abnormal bone scans. This should be considered when interpreting bone-imaging results.

Special precautions in patients undergoing PBPC mobilisation

Mobilisation
There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of $CD34^+$ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an optimum method. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Prior exposure to cytotoxic agents
Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield ($\geq 2.0 \times 10^6$ $CD34^+$ cells/kg) or acceleration of platelet recovery to the same degree.

Some cytotoxic agents exhibit particular toxicities to the haematopoietic progenitor pool and may adversely affect progenitor mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilisation, may reduce progenitor yield. However, the administration of melphalan, carboplatin or carmustine (BCNU) together with filgrastim has been shown to be effective for progenitor mobilisation. When a PBPC transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

Assessment of progenitor cell yields
In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of $CD34^+$ cell numbers vary depending on the precise methodology used and recommendations of numbers based on studies in other laboratories need to be interpreted with caution.

Statistical analysis of the relationship between the number of $CD34^+$ cells re-infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship.

The recommendation of a minimum yields of $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg is based on published experience resulting in adequate haematologic reconstitution. Yields in excess of this appear to correlate with more rapid recovery, those below with slower recovery.

Special precautions in normal donors undergoing PBPC mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to haematological values and infectious diseases.

The safety and efficacy of filgrastim has not been assessed in normal donors less than 16 years or greater than 60 years.

Transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets < 50 x 10^9/L were reported and attributed to the leukapheresis procedure.

If more than one leukapheresis is required, particular attention should be paid to donors with platelets < 100 x 10^9/L prior to leukapheresis; in general apheresis should not be performed if platelets are < 75 x 10^9/L.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis. Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.

Special precautions in recipients of allogeneic PBPC mobilised with filgrastim

Current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic GvHD when compared with bone marrow transplantation.

Special precautions in SCN patients

Filgrastim should not be administered to patients with severe congenital neutropenia who develop leukaemia or have evidence of leukaemic evolution.

Blood cell counts
Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.

Transformation to leukaemia or myelodysplastic syndrome
Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia and myeloid leukaemia. Complete blood cell counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukaemias are natural complications of the disease and are of uncertain relation to filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. It is currently unclear whether long-term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions
Causes of transient neutropenia such as viral infections should be excluded.

Haematuria was common and proteinuria occurred in a small number of patients. Regular urinalysis should be performed to monitor these events.

The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established.

Special precautions in patients with HIV infection

Blood cell counts
Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 µg) /day of filgrastim, there can be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples are taken for ANC measurement immediately prior to any scheduled dosing with filgrastim.

Risk associated with increased doses of myelosuppressive medicinal products
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medicinal products. As a result of the potential to receive higher doses or a greater number of these medicinal products with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

Infections and malignancies causing myelosuppression
Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infections or malignancy, consider appropriate therapy for treatment of the underlying condition in addition to administration of filgrastim for treatment of neutropenia. The effects of filgrastim on neutropenia due to bone marrow-infiltrating infection or malignancy have not been well established.

All patients

Accofil contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.
Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Accofil contains less than 1mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

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

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of filgrastim given on the same day as myelosuppressive cytotoxic chemotherapy have not been definitively established. In view of the sensitivity of rapidly dividing

myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of filgrastim is not recommended in the period from 24 hours before to 24 hours after chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with filgrastim and 5-Fluorouracil indicates that the severity of neutropenia may be exacerbated.

Possible interactions with other haematopoietic growth factors and cytokines have not yet been investigated in clinical trials.

Since lithium promotes the release of neutrophils, lithium is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3). There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.

Filgrastim is not recommended during pregnancy.

Breast-feeding

It is unknown whether filgrastim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from filgrastim therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Filgrastim did not affect reproductive performance or fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Accofil may have a minor influence on the ability to drive and use machines.

Dizziness may occur following the administration of Accofil (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse reactions that may occur during Filgrastim treatment include: anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, severe splenomegaly/splenic rupture, transformation to myelodysplastic syndrome or leukaemia in SCN patients, GvHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant and sickle cell crisis in patients with sickle cell disease.

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea. In clinical trials in cancer patients musculoskeletal pain was mild or moderate in 10%, and severe in 3% of patients.

b. Tabulated summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	**Adverse reactions**			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia Anaemia[e]	Splenomegaly[a] Haemoglobin decreased[e]	Leukocytosis[a]	Splenic rupture[a] Sickle cell anaemia with crisis Extramedullary haematopoiesis
Immune system disorders			Hypersensitivity Drug hypersensitivity[a] Graft versus host disease[b]	Anaphylactic reaction
Metabolism and nutrition disorders		Decreased appetite[e] Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout[a] (Chondrocalcinosis Pyrophosphate) Fluid volume disturbances
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache[a]	Dizziness, Hypoaesthesia, Paraesthesia		
Vascular disorders		Hypotension Hypertension	Veno-occlusive disease[d]	Capillary leak syndrome[a] Aortitis
Respiratory, thoracic and mediastinal disorders		Haemoptysis Dyspnoea Cough[a] Oropharyngeal pain[a,e] Epistaxis	Acute respiratory distress syndrome[a] Respiratory failure[a]	

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
			Pulmonary oedema[a] Interstitial lung disease[a] Lung infiltration[a] Pulmonary haemorrhage Hypoxia	
Gastrointestinal disorders	Diarrhoea[a,e] Vomiting[a,e] Nausea[a]	Constipation[e] Oral pain		
Hepatobiliary disorders		Blood alkaline phosphatase increased Hepatomegaly	Gamma-glutamyl transferase increased Aspartate aminotransferase increased	
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Rash maculopapular	Sweets syndrome (acute febrile neutrophilic dermatosis) Cutaneous vasculitis[a]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[c]	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Urine abnormality Glomerulonephritis
General disorders and administration site conditions	Fatigue[a] Mucosal inflammation[a] Pyrexia	Chest pain[a] Asthenia[a] Pain[a] Malaise[e] Oedema peripheral[e]	Injection site reaction	
Injury, poisoning and procedural complications		Transfusion reaction[e]		

[a] See section c (Description of selected adverse reactions)
[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section c)
[c] Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

[d] Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC mobilisation
[e] Adverse events with higher incidence in Filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy

c. Description of selected adverse reactions

GvHD
There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see sections 4.4 and 5.1).

Capillary leak syndrome
Cases of capillary leak syndrome have been reported with granulocyte-colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

Sweets syndrome
Cases of Sweets syndrome (acute febrile neutrophilic dermatosis) have been reported in patients treated with filgrastim.

Pulmonary adverse events
In clinical studies and the post-marketing setting pulmonary adverse effects including interstitial lung disease, pulmonary oedema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4)

Splenomegaly and Splenic rupture
Cases of splenomegaly and splenic rupture have been reported following administration of filgrastim. Some cases of splenic rupture were fatal (see section 4.4).

Hypersensitivity
Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post-marketing experience. Overall, reports were more common after IV administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Cutaneous vasculitis
Cutaneous vasculitis has been reported in patients treated with Filgrastim. The mechanism of vasculitis in patients receiving Filgrastim is unknown. During long term use cutaneous vasculitis has been reported in 2% of SCN patients.

Pseudogout (chondrocalcinosis pyrophosphate)
Pseudogout (chondrocalcinosis pyrophosphate) has been reported in cancer patients treated with filgrastim.

Leukocytosis
Leukocytosis (WBC > 50 x 10^9/L) was observed in 41% of normal donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35% of donors (see section 4.4).

d. Paediatric population

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy suggesting no age-related differences in the pharmacokinetics of filgrastim. The only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

There is insufficient data to further evaluate filgrastim use in paediatric subjects.

e. Other special populations

Geriatric Use
No overall differences in safety or effectiveness were observed between subjects over 65 years of age compared to younger adult (>18 years of age) subjects receiving cytotoxic chemotherapy and clinical experience has not identified differences in the responses between elderly and younger adult patients. There is insufficient data to evaluate Accofil use in geriatric subjects for other approved Accofil indications.

Paediatric SCN patients
Cases of decreased bone density and osteoporosis have been reported in paediatric patients with severe chronic neutropenia receiving chronic treatment with filgrastim.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The effects of Accofil overdosage have not been established. Discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factors, ATC code: L03AA02
Accofil is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Accofil containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes. In some SCN patients, filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.

Use of filgrastim in patients undergoing cytotoxic chemotherapy leads to significant reductions in the incidence, severity and duration of neutropenia and febrile neutropenia. Treatment with filgrastim significantly reduces the duration of febrile neutropenia, antibiotic use and hospitalisation after induction chemotherapy for acute myelogenous leukaemia or myeloablative therapy followed by bone marrow transplantation. The incidence of fever and documented infections were not reduced in either setting. The duration of fever was not reduced in patients undergoing myeloablative therapy followed by bone marrow transplantation.

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into the peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic

therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

Recipients of allogeneic PBPCs mobilised with filgrastim experienced significantly more rapid haematological recovery, leading to a significant decrease in time to unsupported platelet recovery when compared with allogeneic bone marrow transplantation.

One retrospective European study evaluating the use of G-CSF after allogeneic bone marrow transplantation in patients with acute leukaemias suggested an increase in the risk of GvHD, treatment related mortality (TRM) and mortality when G-CSF was administered. In a separate retrospective international study in patients with acute and chronic myelogenous leukaemias, no effect on the risk of GvHD, TRM and mortality was seen. A meta-analysis of allogeneic transplant studies, including the results of nine prospective randomized trials, 8 retrospective studies and 1 case-controlled study, did not detect an effect on the risks of acute GvHD, chronic GvHD or early treatment-related mortality.

Relative risk (95% CI) of GvHD and TRM following treatment with G-CSF after bone marrow (BM) transplantation					
Publication	**Period of Study**	**N**	**Acute Grade II - IV GvHD**	**Chronic GvHD**	**TRM**
Meta-Analysis (2003)	1986 - 2001[a]	1198	1.08 (0.87, 1.33)	1.02 (0.82, 1.26)	0.70 (0.38, 1.31)
European Retrospective Study (2004)	1992 - 2002[b]	1789	1.33 (1.08, 1.64)	1.29 (1.02, 1.61)	1.73 (1.30, 2.32)
International Retrospective Study (2006)	1995 - 2000[b]	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)

[a] Analysis includes studies involving BM transplant during this period; some studies used GM-CSF

[b] Analysis includes patients receiving BM transplant during this period

Use of filgrastim for the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

In normal donors, a 10 µg/kg/day dose administered subcutaneously for 4 - 5 consecutive days allows a collection of $\geq 4 \times 10^6$ $CD34^+$ cells/kg recipient body weight in the majority of the donors after two leukaphereses.

Use of filgrastim in patients, children or adults, with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in absolute neutrophil counts in peripheral blood and a reduction of infection and related events.

Use of filgrastim in patients with HIV infection maintains normal neutrophil counts to allow scheduled dosing of antiviral and/or other myelosuppressive medication. There is no evidence that patients with HIV infection treated with filgrastim show an increase in HIV replication.

As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration of recommended doses, serum concentrations were maintained above10 ng/ml for 8 - 16 hours.

Distribution

The volume of distribution in blood is approximately 150 ml/kg.

Elimination

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half-life of filgrastim is approximately 3.5 hours, with a clearance rate of approximately 0.6 ml/min/kg. Continuous infusion with Accofil over a period of up to 28 days, in patients recovering from autologous bone-marrow transplantation, resulted in no evidence of drug accumulation and comparable elimination half-lives.

Linearity

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

5.3 Preclinical safety data

Filgrastim was studied in repeated dose toxicity studies up to 1 year in duration which revealed changes attributable to the expected pharmacological actions including increases in leucocytes , myeloid hyperplasia in bone marrow, extramedullary granulopoiesis and splenic enlargement. These changes all reversed after discontinuation of treatment.
Effects of filgrastim on prenatal development have been studied in rats and rabbits. Intravenous (80 µg/kg/day) administration of filgrastim to rabbits during the period of organogenesis was maternally toxic and increased spontaneous abortion, post-implantation loss, and decreased mean live litter size and foetal weight were observed.
Based on reported data for another filgrastim product similar to Accofil, comparable findings plus increased foetal malformations were observed at 100 µg/kg/day, a maternally toxic dose which corresponded to a systemic exposure of approximately 50-90 times the exposures observed in patients treated with the clinical dose of 5 µg/kg/day. The no observed adverse effect level for embryo-foetal toxicity in this study was 10 µg/kg/day, which corresponded to a systemic exposure of approximately 3-5 times the exposures observed in patients treated with the clinical dose.
In pregnant rats, no maternal or foetal toxicity was observed at doses up to 575 µg/kg/day. Offspring of rats administered filgrastim during the peri-natal and lactation periods, exhibited a delay in external differentiation and growth retardation (≥20 µg/kg/day) and slightly reduced survival rate (100 µg/kg/day).
Filgrastim had no observed effect on the fertility of male or female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid glacial
Sodium hydroxide
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

Accofil must not be diluted with sodium chloride solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

This medicinal product must not be mixed with other products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

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

Within its shelf-life and for the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 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 syringe in the outer carton in order to protect from light.

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.

6.5 Nature and contents of container

Type I glass pre-filled syringe with a permanently attached stainless steel needle in the tip and 1/40 printed markings for graduations from 0.1 mL to 1 mL on the barrel. The needle cover of the pre-filled syringe contains dry natural rubber (see section 4.4). Each pre-filled syringe contains 0.5 ml solution.

Each pack contains one, three, five, seven or ten pre-filled syringes, with or without a needle safety guard, and alcohol swabs. The packs without blister are for syringes without needle safety guard. The blister packs are for individual syringes with prefixed needle safety guard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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. Do not shake.

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.

Accofil contains no preservative. In view of the possible risk of microbial contamination, Accofil pre-filled syringes are for single use only.

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

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.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/003
EU/1/14/946/004
EU/1/14/946/011
EU/1/14/946/012
EU/1/14/946/013
EU/1/14/946/014
EU/1/14/946/015
EU/1/14/946/016
EU/1/14/946/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 18.09.2014
Date of latest renewal: 12th June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Accofil 12 MU/0.2 mL solution for injection/infusion in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 12 million units (MU)/ 120 micrograms (µg) of filgrastim in 0.2 ml (0.6 mg/ml) solution for injection or infusion.

Filgrastim is a recombinant methionyl human granulocyte-colony stimulating factor produced in *Escherichia coli* (BL21) by recombinant DNA technology.

Excipient with known effect:

Each ml of solution contains 50 mg of sorbitol (E420)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or in pre-filled syringe

Concentrate for solution for infusion in pre-filled syringe

Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Accofil is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of Accofil are similar in adults and children receiving cytotoxic chemotherapy.

Accofil is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs).

In patients, children or adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, long term administration of Accofil is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Accofil is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

4.2 Posology and method of administration

Accofil therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration

with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

The Accofil 12 MU/0.2 mL prefilled syringe is specially designed to allow administration of doses equal to or less than 12MU in paediatric patients. The syringe bears graduation marks (major graduations at 0.1 mL and minor graduations at 0.025 mL up to 1.0 mL) which are necessary to accurately measure doses of Accofil equal to or less than 12MU, to meet to individual dosing requirements in paediatric patients.

Posology

Established cytotoxic chemotherapy
The recommended dose of filgrastim is 0.5 MU (5 µg)/kg/day. The first dose of Accofil should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 µg/m^2/day (4.0 to 8.4 µg/kg/day) was used.

Daily dosing with filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, lymphomas, and lymphoid leukaemia, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days. Following induction and consolidation treatment for acute myeloid leukaemia the duration of treatment may be substantially longer (up to 38 days) depending on the type, dose and schedule of cytotoxic chemotherapy used.

In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1-2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of filgrastim therapy, prior to the time of the expected neutrophil nadir, is not recommended.

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of filgrastim is 1.0 MU (10 µg)/kg/day. The first dose of filgrastim should be administered at least 24 hours following cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

Once the neutrophil nadir has been passed, the daily dose of filgrastim should be titrated against the neutrophil response as follows:

Neutrophil count	**Filgrastim dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 0.5 MU (5 µg)/kg/day
Then, if ANC remains > 1.0 x 10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0 x 10^9/L during the treatment period, the dose of filgrastim should be re-escalated according to the above steps	

ANC = absolute neutrophil count

For mobilisation of peripheral blood progenitor cells (PBPC) in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU (10 µg)/kg/day for 5-7 consecutive days. Timing of leukapheresis: 1 or 2 leukapheresis on days 5 and 6 are often sufficient. In other circumstances, additional leukapheresis may be necessary. Filgrastim dosing should be maintained until the last leukapheresis.

The recommended dose of filgrastim for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MU (5 µg)/kg/day from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis

should be performed during the period when the ANC rises from
< 0.5 x 10^9/L to > 5.0 x 10^9/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis are recommended.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation
For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU (10 µg)/kg/day for 4 to 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4 x 10^6 $CD34^+$ cells/kg recipient bodyweight.

In patients with severe chronic neutropenia (SCN)
Congenital neutropenia
The recommended starting dose is 1.2 MU (12 µg)/kg/day as a single dose or in divided doses.

Idiopathic or cyclic neutropenia
The recommended starting dose is 0.5 MU (5 µg)/kg/day as a single dose or in divided doses.

Dose adjustments
Filgrastim should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than 1.5 x 10^9/L. When the response has been obtained, the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently, the dose may be individually adjusted every 1 to 2 weeks to maintain the average neutrophil count between 1.5 x 10^9/L and 10 x 10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97% of patients who responded had a complete response at doses of ≤ 24 µg/kg/day. The long-term safety of administration of filgrastim at doses above 24 µg/kg/day in patients with SCN has not been established.

In patients with HIV infection

For reversal of neutropenia
The recommended starting dose of filgrastim is 0.1 MU (1 µg)/kg/day, with titration up to a maximum of 0.4 MU (4 µg)/kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0 x 10^9/L). In clinical studies, more than 90% of patients responded at these doses, achieving reversal of neutropenia in a median of 2 days.

In a small number of patients (< 10%), doses up to 1.0 MU (10 µg)/kg/day were required to achieve reversal of neutropenia.

For maintenance of normal neutrophil counts
When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU (300 µg)/day is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2.0 x 10^9/L. In clinical studies, dosing with 30 MU (300 µg)/day on 1 - 7 days per week was required to maintain the ANC > 2.0 x 10^9/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC > 2.0 x 10^9/L.

Special population
Elderly

Clinical trials with filgrastim have included a small number of elderly patients but special studies have not been performed in this group and therefore specific dosage recommendations cannot be made.

Patients with renal impairment

Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.

Paediatric use in the SCN and cancer settings
Sixty-five percent of the patients studied in the SCN trial programme were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for SCN.

Data from clinical studies in paediatric patients indicate that the safety and efficacy of Filgrastim are similar in both adults and children receiving cytotoxic chemotherapy.

The dosage recommendations in paediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy.

Method of administration

Established cytotoxic chemotherapy
Filgrastim may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minute (see section 6.6). The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance.

In patients treated with myeloablative therapy followed by bone marrow transplantation
Filgrastim may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 mL of 5% glucose solution (see section 6.6).

For the mobilisation of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation
Filgrastim for PBPC mobilisation when used alone:
Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions filgrastim should be diluted in 20ml of 5% glucose solution (see section 6.6).

Filgrastim for PBPC mobilisation after myelosuppressive chemotherapy
Filgrastim should be given by subcutaneous injection.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation
Filgrastim should be given by subcutaneous injection.

In patients with severe chronic neutropenia (SCN)
Congenital, idiopathic or cyclic neutropenia, filgrastim should be given by subcutaneous injection.

In patients with HIV infection
Reversal of neutropenia and maintaining of normal neutrophil counts: filgrastim should be given by subcutaneous injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number

of the administered product should be clearly recorded.

Special warning and precautions across indications

Hypersensitivity
Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with filgrastim. Permanently discontinue filgrastim in patients with clinically significant hypersensitivity. Do not administer filgrastim to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Pulmonary adverse effects
Pulmonary adverse effects, in particular interstitial lung disease, have been reported after G-CSF administration. Patients with a recent history of lung infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given.

Glomerulonephritis
Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Capillary leak syndrome
Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after granulocyte-colony stimulating factor administration, and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see section 4.8).

Splenomegaly and splenic rupture
Generally asymptomatic cases of splenomegaly and cases of splenic rupture have been reported in patients and normal donors following administration of filgrastim. Some cases of splenic rupture were fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal or shoulder tip pain. Dose reductions of Filgrastim have been noted to slow or stop the progression of splenic enlargement in patients with severe chronic neutropenia, and in 3% of patients a splenectomy was required.

Malignant cell growth
Granulocyte-colony stimulating factor can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

Myelodysplastic syndrome or Chronic myeloid leukaemia
The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia have not been established. Filgrastim is not indicated for use in these conditions. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

Acute myeloid leukaemia
In view of limited safety and efficacy data in patients with secondary AML, filgrastim should be administered with caution. The safety and efficacy of filgrastim administration in *de novo* AML patients aged < 55 years with good cytogenetics [t (8; 21), t (15; 17), and inv (16)] have not been established.

Thrombocytopenia
Thrombocytopenia has been reported in patients receiving filgrastim. Platelet counts should be

monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to temporary discontinuation or dose reduction of filgrastim in patients with severe chronic neutropenia who develop thrombocytopenia (platelet count < 100 × 10^9/L).

Leukocytosis
White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5% of cancer patients receiving filgrastim at doses above 0.3 MU/kg/day (3 µg/kg/day). No undesirable effects directly attributable to this degree of leukocytosis have been reported. However, in view of the potential risks associated with severe leukocytosis, a white blood cell count should be performed at regular intervals during filgrastim therapy. If leukocyte counts exceed 50 x 10^9/L after the expected nadir, filgrastim should be discontinued immediately. When administered for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against filgrastim is generally low. Binding antibodies do occur as expected with all biologics; However, they have not been associated with neutralising activity at present.

Aortitis
Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also section 4.8.

Special warnings and precautions associated with co-morbidities

Special precautions in sickle cell trait and sickle cell disease
Sickle cell crises, in some cases fatal, have been reported with the use of filgrastim in patients with sickle cell trait or sickle cell disease. Physicians should use caution when prescribing filgrastim in patients with sickle cell trait or sickle cell disease.

Osteoporosis
Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with filgrastim for more than 6 months.

Special precautions in cancer patients

Filgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Risks associated with increased doses of chemotherapy
Special caution should be used when treating patients with high-dose chemotherapy because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the prescribing information of the specific chemotherapy agents used).

Effect of chemotherapy on erythrocytes and thrombocytes
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Because of the potential of receiving higher doses of chemotherapy (e.g. full doses on the prescribed schedule) the patient may be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

The use of filgrastim-mobilised PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Myelodysplastic syndrome and acute myeloid leukaemia in breast and lung cancer patients
In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim, an alternative G-CSF medicine, in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association between filgrastim and MDS/AML has not been observed. Nonetheless, patients with breast cancer and patients with lung cancer should be monitored for signs and symptoms of MDS/AML.

Other special precautions
The effects of filgrastim in patients with substantially reduced myeloid progenitors have not been studied. Filgrastim acts primarily on neutrophil precursors to exert its effect in elevating neutrophil counts. Therefore, in patients with reduced precursors, neutrophil response may be diminished (such as those treated with extensive radiotherapy or chemotherapy, or those with bone marrow infiltration by tumour).

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high-dose chemotherapy followed by transplantation.

There have been reports of graft versus host disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 4.8 and 5.1).

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient abnormal bone scans. This should be considered when interpreting bone-imaging results.

Special precautions in patients undergoing PBPC mobilisation

Mobilisation
There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of $CD34^+$ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an optimum method. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Prior exposure to cytotoxic agents
Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield ($\geq 2.0 \times 10^6$ $CD34^+$ cells/kg) or acceleration of platelet recovery to the same degree.

Some cytotoxic agents exhibit particular toxicities to the haematopoietic progenitor pool and may adversely affect progenitor mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilisation, may reduce progenitor yield. However, the administration of melphalan, carboplatin or carmustine (BCNU) together with filgrastim has been shown to be effective for progenitor mobilisation. When a PBPC transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

Assessment of progenitor cell yields
In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of $CD34^+$ cell numbers vary depending on the precise methodology used and recommendations of numbers based on studies in other laboratories need to be interpreted with caution.

Statistical analysis of the relationship between the number of $CD34^+$ cells re-infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship.

The recommendation of a minimum yields of $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg is based on published experience resulting in adequate haematologic reconstitution. Yields in excess of this appear to correlate with more rapid recovery, those below with slower recovery.

Special precautions in normal donors undergoing PBPC mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to haematological values and infectious diseases. The safety and efficacy of filgrastim has not been assessed in normal donors less than 16 years or greater than 60 years.

Transient thrombocytopenia (platelets $< 100 \times 10^9$/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets $< 50 \times 10^9$/L were reported and attributed to the leukapheresis procedure.

If more than one leukapheresis is required, particular attention should be paid to donors with platelets $< 100 \times 10^9$/L prior to leukapheresis; in general apheresis should not be performed if platelets $< 75 \times 10^9$/L.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis. Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.

Special precautions in recipients of allogeneic PBPCs mobilised with filgrastim

Current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic GvHD when compared with bone marrow transplantation.

Special precautions in SCN patients

Filgrastim should not be administered to patients with severe congenital neutropenia who develop leukaemia or have evidence of leukaemic evolution.

Blood cell counts
Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.

Transformation to leukaemia or myelodysplastic syndrome
Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia and myeloid leukaemia. Complete blood cell counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukaemias are natural complications of the disease and are of uncertain relation to filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. It is currently unclear whether long-term treatment of

patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions
Causes of transient neutropenia such as viral infections should be excluded.
Haematuria was common and proteinuria occurred in a small number of patients. Regular urinalysis should be performed to monitor these events.

The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established.

Special precautions in patients with HIV infection

Blood cell counts
Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 µg)/day of filgrastim, there can be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples are taken for ANC measurement immediately prior to any scheduled dosing with filgrastim.

Risk associated with increased doses of myelosuppressive medicinal products
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medicinal products. As a result of the potential to receive higher doses or a greater number of these medicinal products with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

Infections and malignancies causing myelosuppression
Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infections or malignancy, consider appropriate therapy for treatment of the underlying condition in addition to administration of filgrastim for treatment of neutropenia. The effects of filgrastim on neutropenia due to bone marrow-infiltrating infection or malignancy have not been well established.

All patients

Accofil contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.
Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Accofil contains less than 1mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

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

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of filgrastim given on the same day as myelosuppressive cytotoxic chemotherapy have not been definitively established. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of filgrastim is not recommended in the period from 24 hours before to 24 hours after chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with filgrastim and 5-Fluorouracil indicates that the severity of neutropenia may be exacerbated.

Possible interactions with other haematopoietic growth factors and cytokines have not yet been investigated in clinical trials.

Since lithium promotes the release of neutrophils, lithium is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3). There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.

Filgrastim is not recommended during pregnancy.

Breast-feeding

It is unknown whether filgrastim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from filgrastim therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Filgrastim did not affect reproductive performance or fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Accofil may have a minor influence on the ability to drive and use machines.

Dizziness may occur following the administration of Accofil (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse reactions that may occur during Filgrastim treatment include: anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, severe splenomegaly/splenic rupture, transformation to myelodysplastic syndrome or leukaemia in SCN patients, GvHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant and sickle cell crisis in patients with sickle cell disease.

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes

bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea. In clinical trials in cancer patients musculoskeletal pain was mild or moderate in 10%, and severe in 3% of patients.

b. Tabulated summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	**Adverse reactions**			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia Anaemia[e]	Splenomegaly[a] Haemoglobin decreased[e]	Leukocytosis[a]	Splenic rupture[a] Sickle cell anaemia with crisis Extramedullary haematopoiesis
Immune system disorders			Hypersensitivity Drug hypersensitivity[a] Graft versus host disease[b]	Anaphylactic reaction
Metabolism and nutrition disorders		Decreased appetite[e] Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout[a] (Chondrocalcinosis Pyrophosphate) Fluid volume disturbances
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache[a]	Dizziness, Hypoaesthesia, Paraesthesia		
Vascular disorders		Hypotension Hypertension	Veno-occlusive disease[d]	Capillary leak syndrome[a], Aortitis
Respiratory, thoracic and		Haemoptysis Dyspnoea Cough[a] Oropharyngeal	Acute respiratory distress syndrome[a]	

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
mediastinal disorders		pain[a,e] Epistaxis	Respiratory failure[a] Pulmonary oedema[a] Interstitial lung disease[a] Lung infiltration[a] Pulmonary haemorrhage Hypoxia	
Gastrointestinal disorders	Diarrhoea[a,e] Vomiting[a,e] Nausea[a]	Constipation[e] Oral pain		
Hepatobiliary disorders		Blood alkaline phosphatase increased Hepatomegaly	Gamma-glutamyl transferase increased Aspartate aminotransferase increased	
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Rash maculopapular	Sweets syndrome (acute febrile neutrophilic dermatosis) Cutaneous vasculitis[a]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[c]	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Urine abnormality Glomerulonephritis
General disorders and administration site conditions	Fatigue[a] Mucosal inflammation[a] Pyrexia	Chest pain[a] Asthenia[a] Pain[a] Malaise[e] Oedema peripheral[e]	Injection site reaction	
Injury, poisoning and procedural complications		Transfusion reaction[e]		

[a] See section c (Description of selected adverse reactions)

[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section c)
[c] Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain
[d] Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC mobilisation
[e] Adverse events with higher incidence in Filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy

c. Description of selected adverse reactions

GvHD
There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see sections 4.4 and 5.1).

Capillary leak syndrome
Cases of capillary leak syndrome have been reported with granulocyte-colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

Sweets syndrome
Cases of Sweets syndrome (acute febrile neutrophilic dermatosis) have been reported in patients treated with filgrastim.

Pulmonary adverse events
In clinical studies and the post-marketing setting pulmonary adverse effects including interstitial lung disease, pulmonary oedema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4)

Splenomegaly and Splenic rupture
Cases of splenomegaly and splenic rupture have been reported following administration of filgrastim. Some cases of splenic rupture were fatal (see section 4.4).

Hypersensitivity
Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post-marketing experience. Overall, reports were more common after IV administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Cutaneous vasculitis
Cutaneous vasculitis has been reported in patients treated with Filgrastim. The mechanism of vasculitis in patients receiving Filgrastim is unknown. During long term use cutaneous vasculitis has been reported in 2% of SCN patients.

Pseudogout (chondrocalcinosis pyrophosphate)
Pseudogout (chondrocalcinosis pyrophosphate) has been reported in cancer patients treated with filgrastim.

Leukocytosis
Leukocytosis (WBC > 50 x 10^9/L) was observed in 41% of normal donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35% of donors (see section 4.4).

d. Paediatric population

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy suggesting no age-related differences in the pharmacokinetics of filgrastim. The only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

There is insufficient data to further evaluate filgrastim use in paediatric subjects.

e. Other special populations

Geriatric use
No overall differences in safety or effectiveness were observed between subjects over 65 years of age compared to younger adult (>18 years of age) subjects receiving cytotoxic chemotherapy and clinical experience has not identified differences in the responses between elderly and younger adult patients. There is insufficient data to evaluate Accofil use in geriatric subjects for other approved Accofil indications.

Paediatric SCN patients
Cases of decreased bone density and osteoporosis have been reported in paediatric patients with severe chronic neutropenia receiving chronic treatment with filgrastim.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The effects of Accofil overdosage have not been established. Discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factors, ATC code: L03AA02
Accofil is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Accofil containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes. In some SCN patients, filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.

Use of filgrastim in patients undergoing cytotoxic chemotherapy leads to significant reductions in the incidence, severity and duration of neutropenia and febrile neutropenia. Treatment with filgrastim significantly reduces the duration of febrile neutropenia, antibiotic use and hospitalisation after

induction chemotherapy for acute myelogenous leukaemia or myeloablative therapy followed by bone marrow transplantation. The incidence of fever and documented infections were not reduced in either setting. The duration of fever was not reduced in patients undergoing myeloablative therapy followed by bone marrow transplantation.

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into the peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

Recipients of allogeneic PBPCs mobilised with filgrastim experienced significantly more rapid haematological recovery, leading to a significant decrease in time to unsupported platelet recovery when compared with allogeneic bone marrow transplantation.

One retrospective European study evaluating the use of G-CSF after allogeneic bone marrow transplantation in patients with acute leukaemias suggested an increase in the risk of GvHD, treatment related mortality (TRM) and mortality when G-CSF was administered. In a separate retrospective international study in patients with acute and chronic myelogenous leukaemias, no effect on the risk of GvHD, TRM and mortality was seen. A meta-analysis of allogeneic transplant studies, including the results of nine prospective randomized trials, 8 retrospective studies and 1 case-controlled study, did not detect an effect on the risks of acute GvHD, chronic GvHD or early treatment-related mortality.

Relative risk (95% CI) of GvHD and TRM following treatment with G-CSF after bone marrow (BM) transplantation					
Publication	**Period of Study**	**N**	**Acute Grade II - IV GvHD**	**Chronic GvHD**	**TRM**
Meta-Analysis (2003)	1986 - 2001[a]	1198	1.08 (0.87, 1.33)	1.02 (0.82, 1.26)	0.70 (0.38, 1.31)
European Retrospective Study (2004)	1992 - 2002[b]	1789	1.33 (1.08, 1.64)	1.29 (1.02, 1.61)	1.73 (1.30, 2.32)
International Retrospective Study (2006)	1995 - 2000[b]	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)

[a] Analysis includes studies involving BM transplant during this period; some studies used GM-CSF

[b] Analysis includes patients receiving BM transplant during this period

Use of filgrastim for the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

In normal donors, a 10 µg/kg/day dose administered subcutaneously for 4 - 5 consecutive days allows a collection of $\geq 4 \times 10^6$ $CD34^+$ cells/kg recipient body weight in the majority of the donors after two leukaphereses.

Use of filgrastim in patients, children or adults, with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in absolute neutrophil counts in peripheral blood and a reduction of infection and related events.

Use of filgrastim in patients with HIV infection maintains normal neutrophil counts to allow scheduled dosing of antiviral and/or other myelosuppressive medication. There is no evidence that patients with HIV infection treated with filgrastim show an increase in HIV replication.

As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration of recommended doses, serum concentrations were maintained above10 ng/ml for 8 - 16 hours.

Distribution

The volume of distribution in blood is approximately 150 ml/kg.

Elimination

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half-life of filgrastim is approximately 3.5 hours, with a clearance rate of approximately 0.6 ml/min/kg. Continuous infusion with Accofil over a period of up to 28 days, in patients recovering from autologous bone-marrow transplantation, resulted in no evidence of drug accumulation and comparable elimination half-lives.

Linearity

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

5.3 Preclinical safety data

Filgrastim was studied in repeated dose toxicity studies up to 1 year in duration which revealed changes attributable to the expected pharmacological actions including increases in leucocytes, myeloid hyperplasia in bone marrow, extramedullary granulopoiesis and splenic enlargement. These changes all reversed after discontinuation of treatment.
Effects of filgrastim on prenatal development have been studied in rats and rabbits. Intravenous (80 µg/kg/day) administration of filgrastim to rabbits during the period of organogenesis was maternally toxic and increased spontaneous abortion, post-implantation loss, and decreased mean live litter size and foetal weight were observed.
Based on reported data for another filgrastim product similar to Accofil, comparable findings plus increased foetal malformations were observed at 100 µg/kg/day, a maternally toxic dose which corresponded to a systemic exposure of approximately 50-90 times the exposures observed in patients treated with the clinical dose of 5 µg/kg/day. The no observed adverse effect level for embryo-foetal toxicity in this study was 10 µg/kg/day, which corresponded to a systemic exposure of approximately 3-5 times the exposures observed in patients treated with the clinical dose.
In pregnant rats, no maternal or foetal toxicity was observed at doses up to 575 µg/kg/day. Offspring of rats administered filgrastim during the peri-natal and lactation periods, exhibited a delay in external differentiation and growth retardation (≥20 µg/kg/day) and slightly reduced survival rate (100 µg/kg/day).
Filgrastim had no observed effect on the fertility of male or female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid glacial
Sodium hydroxide
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

Accofil must not be diluted with sodium chloride solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

This medicinal product must not be mixed with other products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

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

Within its shelf-life and for the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 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 syringe in the outer carton in order to protect from light.

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.

6.5 Nature and contents of container

Type I glass pre-filled syringe with a permanently attached stainless steel needle in the tip and 1/40 printed markings for graduations from 0.1 mL to 1 mL on the barrel. The needle cover of the pre-filled syringe contains dry natural rubber (see section 4.4). Each pre-filled syringe contains 0.2 ml solution.

Each pack contains one, three, five, seven or ten pre-filled syringes, with or without a needle safety guard, and alcohol swab(s). The packs without blister are for syringes without needle safety guard. The blister packs are for individual syringes with prefixed needle safety guard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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. Do not shake.

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.

Accofil contains no preservative. In view of the possible risk of microbial contamination, Accofil pre-filled syringes are for single use only.

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

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.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/19
EU/1/14/946/20
EU/1/14/946/21
EU/1/14/946/22
EU/1/14/946/23
EU/1/14/946/24
EU/1/14/946/25
EU/1/14/946/26
EU/1/14/946/27

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 18.09.2014
Date of latest renewal: 12th June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Accofil 70 MU/0.73 ml solution for injection/infusion in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 70 million units (MU)/ 700 micrograms (µg) of filgrastim in 0.73 ml (0.96 mg/ml) solution for injection or infusion.

Filgrastim is a recombinant methionyl human granulocyte-colony stimulating factor produced in *Escherichia coli* (BL21) by recombinant DNA technology.

Excipient with known effect:

Each ml of solution contains 50 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe

Concentrate for solution for infusion in pre-filled syringe

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Accofil is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of Accofil are similar in adults and children receiving cytotoxic chemotherapy.

Accofil is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs).

In patients, children or adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, long term administration of Accofil is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Accofil is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

4.2 Posology and method of administration

Accofil therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration

with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

The Accofil 70 MU/0.73 mL prefilled syringe is specially designed to allow administration of Filgrastim doses of 10 µg/kg/day in adult patients, thus minimising the number of administrations required with multiple pre-filled syringes of 30 MU/0.5 mL and 48 MU/0.5 mL, in the below settings:

- Non-chemotherapy related peripheral blood progenitor cells (PBPC) mobilisation for autologous PBPC transplantation
- PBPC mobilisation following myelosuppressive chemotherapy
- For the mobilisation of PBPC in normal volunteers for use in allogeneic PBPC transplantation
- For the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation

Posology

Established cytotoxic chemotherapy
The recommended dose of filgrastim is 0.5 MU (5 µg)/kg/day. The first dose of Accofil should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 µg/m^2/day (4.0 to 8.4 µg/kg/day) was used.

Daily dosing with filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, lymphomas, and lymphoid leukaemia, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days. Following induction and consolidation treatment for acute myeloid leukaemia the duration of treatment may be substantially longer (up to 38 days) depending on the type, dose and schedule of cytotoxic chemotherapy used.

In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1-2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of filgrastim therapy, prior to the time of the expected neutrophil nadir, is not recommended.

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of filgrastim is 1.0 MU (10 µg)/kg/day. The first dose of filgrastim should be administered at least 24 hours following cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

Once the neutrophil nadir has been passed, the daily dose of filgrastim should be titrated against the neutrophil response as follows:

Neutrophil count	**Filgrastim dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 0.5 MU (5 µg)/kg/day
Then, if ANC remains > 1.0 x 10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0 x 10^9/L during the treatment period, the dose of filgrastim should be re-escalated according to the above steps	

ANC = absolute neutrophil count

For mobilisation of PBPC in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU (10 µg)/kg/day for 5-7 consecutive days. Timing of leukapheresis: 1 or 2 leukapheresis on days 5 and 6

which is often sufficient. In other circumstances, additional leukapheresis may be necessary. Filgrastim dosing should be maintained until the last leukapheresis.

The recommended dose of filgrastim for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MU (5 µg)/kg/day from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from $< 0.5 \times 10^9$/L to $> 5.0 \times 10^9$/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis are recommended.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU (10 µg)/kg/day for 4 to 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4 x 106 CD34+ cells/kg recipient bodyweight.

In patients with severe chronic neutropenia (SCN)

Congenital neutropenia
The recommended starting dose is 1.2 MU (12 µg)/kg/day as a single dose or in divided doses.

Idiopathic or cyclic neutropenia
The recommended starting dose is 0.5 MU (5 µg)/kg/day as a single dose or in divided doses.

Dose adjustments
Filgrastim should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than 1.5×10^9/L. When the response has been obtained, the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently, the dose may be individually adjusted every 1 to 2 weeks to maintain the average neutrophil count between 1.5×10^9/L and 10×10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trial 97% of patients who responded had a complete response at doses of ≤ 24 µg/kg/day. The long-term safety of administration of filgrastim at doses above 24 µg/kg/day in patients with SCN has not been established.

In patients with HIV infection

For reversal of neutropenia
The recommended starting dose of filgrastim is 0.1 MU (1 µg)/kg/day given daily with titration up to a maximum of 0.4 MU (4 µg)/kg/day until a normal neutrophil count is reached and can be maintained (ANC $> 2.0 \times 10^9$/L). In clinical studies, more than 90% of patients responded at these doses, achieving a reversal of neutropenia in a median of 2 days.

In a small number of patients (< 10%), doses up to 1.0 MU (10 µg) /kg/day were required to achieve reversal of neutropenia.

For maintenance of normal neutrophil counts
When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU (300 µg)/day is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at $> 2.0 \times 10^9$/L. In clinical studies, dosing with 30 MU (300 µg)/day on 1 - 7 days per week was required to maintain the ANC $> 2.0 \times 10^9$/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC $> 2.0 \times 10^9$/L.

Special populations
Elderly

Clinical trials with filgrastim have included a small number of elderly patients but special studies have not been performed in this group and therefore specific dosage recommendations cannot be made.

Patients with renal impairment
Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.

Paediatric use in the SCN and cancer settings
Sixty-five percent the patients studied in the SCN trial programme were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for SCN.

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy.

The dosage recommendations in paediatric patients are the same as those in adults receiving myelosuppressive cytotoxic chemotherapy.

Method of administration

Established cytotoxic chemotherapy
Filgrastim may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minute (see section 6.6). The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance.

In patients treated with myeloablative therapy followed by bone marrow transplantation
Filgrastim may be given as 30 minute or as 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 mL of 5% glucose solution (see section 6.6).

For the with mobilisation of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation
Filgrastim for PBPC mobilisation when used alone:
Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions filgrastim should be diluted in 20ml of 5% glucose solution (see section 6.6).

Filgrastim for PBPC mobilisation after myelosuppressive chemotherapy
Filgrastim should be given by subcutaneous injection.

For the mobilisation of PBPC in normal donors prior to allogeneic PBPC transplantation
Filgrastim should be given by subcutaneous injection.

In patients with severe chronic neutropenia (SCN)
For congenital, idiopathic or cyclic neutropenia, filgrastim should be given by subcutaneous injection.

In patients with HIV infection
Reversal of neutropenia and maintaining of normal neutrophil counts: filgrastim should be given by subcutaneous injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Special warning and precautions across indications

Hypersensitivity
Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with filgrastim. Permanently discontinue filgrastim in patients with clinically significant hypersensitivity. Do not administer filgrastim to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Pulmonary adverse effects
Pulmonary adverse effects, in particular interstitial lung disease, have been reported after G-CSF administration. Patients with a recent history of lung infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given.

Glomerulonephritis
Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Capillary leak syndrome
Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after granulocyte-colony stimulating factor administration, and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see section 4.8).

Splenomegaly and splenic rupture
Generally asymptomatic cases of splenomegaly and cases of splenic rupture have been reported in patients and normal donors following administration of filgrastim. Some cases of splenic rupture were fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal or shoulder tip pain. Dose reductions of Filgrastim have been noted to slow or stop the progression of splenic enlargement in patients with severe chronic neutropenia, and in 3% of patients a splenectomy was required.

Malignant cell growth
Granulocyte-colony stimulating factor can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

Myelodysplastic syndrome or Chronic myeloid leukaemia
The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia have not been established. Filgrastim is not indicated for use in these conditions. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

Acute myeloid leukaemia
In view of limited safety and efficacy data in patients with secondary AML, filgrastim should be administered with caution. The safety and efficacy of filgrastim administration in *de novo* AML patients aged < 55 years with good cytogenetics [t (8; 21), t (15; 17), and inv (16)] have not been established.

Thrombocytopenia
Thrombocytopenia has been reported in patients receiving filgrastim. Platelet counts should be monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to temporary discontinuation or dose reduction of filgrastim in patients with severe chronic neutropenia who develop thrombocytopenia (platelet count < 100×10^9/L).

Leukocytosis
White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5% of cancer patients receiving filgrastim at doses above 0.3 MU/kg/day (3 µg/kg/day). No undesirable effects directly attributable to this degree of leukocytosis have been reported. However, in view of the potential risks associated with severe leukocytosis, a white blood cell count should be performed at regular intervals during filgrastim therapy. If leukocyte counts exceed 50 x 10^9/L after the expected nadir, filgrastim should be discontinued immediately. When administered for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against filgrastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

Aortitis
Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also section 4.8.

Special warnings and precautions associated with co-morbidities

Special precautions in sickle cell trait and sickle cell disease
Sickle cell crises, in some cases fatal, have been reported with the use of filgrastim in patients with sickle cell trait or sickle cell disease. Physicians should use caution when prescribing filgrastim in patients with sickle cell trait or sickle cell disease.

Osteoporosis
Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with filgrastim for more than 6 months.

Special precautions in cancer patients

Filgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Risks associated with increased doses of chemotherapy
Special caution should be used when treating patients with high-dose chemotherapy because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic and dermatologic effects (please refer to the prescribing information of the specific chemotherapy agents used).

Effect of chemotherapy on erythrocytes and thrombocytes
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Because of the potential of receiving higher doses of chemotherapy (e.g. full doses on the prescribed schedule) the patient may be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

The use of filgrastim-mobilised PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Myelodysplastic syndrome and acute myeloid leukaemia in breast and lung cancer patients
In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim, an alternative G-CSF medicine, in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association between filgrastim and MDS/AML has not been observed. Nonetheless, patients with breast cancer and patients with lung cancer should be monitored for signs and symptoms of MDS/AML.

Other special precautions
The effects of filgrastim in patients with substantially reduced myeloid progenitors have not been studied. Filgrastim acts primarily on neutrophil precursors to exert its effect in elevating neutrophil counts. Therefore, in patients with reduced precursors, neutrophil response may be diminished (such as those treated with extensive radiotherapy or chemotherapy, or those with bone marrow infiltration by tumour).

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high-dose chemotherapy followed by transplantation.

There have been reports of graft versus host disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 4.8 and 5.1).

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient abnormal bone scans. This should be considered when interpreting bone-imaging results.

Special precautions in patients undergoing PBPC mobilisation

Mobilisation
There are no prospectively randomised comparisons of the two recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between individual patients and between laboratory assays of $CD34^+$ cells mean that direct comparison between different studies is difficult. It is therefore difficult to recommend an optimum method. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Prior exposure to cytotoxic agents
Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield ($\geq 2.0 \times 10^6$ $CD34^+$ cells/kg) or acceleration of platelet recovery to the same degree.

Some cytotoxic agents exhibit particular toxicities to the haematopoietic progenitor pool and may adversely affect progenitor mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilisation, may reduce progenitor yield. However, the administration of melphalan, carboplatin or carmustine (BCNU) together with filgrastim has been shown to be effective for progenitor mobilisation. When a

PBPC transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

Assessment of progenitor cell yields
In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of $CD34^+$ cell numbers vary depending on the precise methodology used and recommendations of numbers based on studies in other laboratories need to be interpreted with caution.

Statistical analysis of the relationship between the number of $CD34^+$ cells re-infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship.

The recommendation of a minimum yields of $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg is based on published experience resulting in adequate haematologic reconstitution. Yields in excess of this appear to correlate with more rapid recovery, those below with slower recovery.

Special precautions in normal donors undergoing PBPC mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to haematological values and infectious diseases. The safety and efficacy of filgrastim has not been assessed in normal donors less than 16 years or greater than 60 years.

Transient thrombocytopenia (platelets $< 100 \times 10^9$/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets $< 50 \times 10^9$/L were reported and attributed to the leukapheresis procedure.

If more than one leukapheresis is required, particular attention should be paid to donors with platelets $< 100 \times 10^9$/L prior to leukapheresis; in general apheresis should not be performed if platelets $< 75 \times 10^9$/L.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis. Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.

Special precautions in recipients of allogeneic PBPCs mobilised with filgrastim

Current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic GvHD when compared with bone marrow transplantation.

Special precautions in SCN patients

Filgrastim should not be administered to patients with severe congenital neutropenia who develop leukaemia or have evidence of leukaemic evolution.

Blood cell counts

Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts.

Transformation to leukaemia or myelodysplastic syndrome
Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia and myeloid leukaemia. Complete blood cell counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukaemias are natural complications of the disease and are of uncertain relation to filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. It is currently unclear whether long-term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions
Causes of transient neutropenia such as viral infections should be excluded.

Haematuria was common and proteinuria occurred in a small number of patients. Regular urinalysis should be performed to monitor these events.

The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established.

<u>Special precautions in patients with HIV infection</u>
Blood cell counts
Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 µg)/day of filgrastim, there can be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples are taken for ANC measurement immediately prior to any scheduled dosing with filgrastim.

Risk associated with increased doses of myelosuppressive medicinal products
Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medicinal products. As a result of the potential to receive higher doses or a greater number of these medicinal products with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended (see above).

Infections and malignancies causing myelosuppression
Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infections or malignancy, consider appropriate therapy for treatment of the underlying condition in addition to administration of filgrastim for treatment of neutropenia. The effects of filgrastim on neutropenia due to bone marrow-infiltrating infection or malignancy have not been well established.

<u>All patients</u>

Accofil contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.
Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-

threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Accofil contains less than 1mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

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

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of filgrastim given on the same day as myelosuppressive cytotoxic chemotherapy have not been definitively established. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, the use of filgrastim is not recommended in the period from 24 hours before to 24 hours after chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with filgrastim and 5-Fluorouracil indicates that the severity of neutropenia may be exacerbated.

Possible interactions with other haematopoietic growth factors and cytokines have not yet been investigated in clinical trials.

Since lithium promotes the release of neutrophils, lithium is likely to potentiate the effect of filgrastim. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3). There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.

Filgrastim is not recommended during pregnancy.

Breast-feeding

It is unknown whether filgrastim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from filgrastim therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Filgrastim did not affect reproductive performance or fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Accofil may have a minor influence on the ability to drive and use machines.

Dizziness may occur following the administration of Accofil (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse reactions that may occur during Filgrastim treatment include: anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, severe splenomegaly/splenic rupture, transformation to myelodysplastic syndrome or leukaemia in SCN patients, GvHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant and sickle cell crisis in patients with sickle cell disease.

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea. In clinical trials in cancer patients musculoskeletal pain was mild or moderate in 10%, and severe in 3% of patients.

b. Tabulated summary of adverse reactions

The data in the table below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	**Adverse reactions**			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection		
Blood and lymphatic system disorders	Thrombocytopenia Anaemia[e]	Splenomegaly[a] Haemoglobin decreased[e]	Leukocytosis[a]	Splenic rupture[a] Sickle cell anaemia with crisis Extramedullary haematopoiesis
Immune system disorders			Hypersensitivity Drug hypersensitivity[a] Graft versus host disease[b]	Anaphylactic reaction
Metabolism and nutrition disorders		Decreased appetite[e] Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout[a] (Chondrocalcinosis Pyrophosphate) Fluid volume disturbances
Psychiatric disorders		Insomnia		

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
Nervous system disorders	Headache[a]	Dizziness, Hypoaesthesia, Paraesthesia		
Vascular disorders		Hypotension Hypertension	Veno-occlusive disease[d]	Capillary leak syndrome[a] Aortitis
Respiratory, thoracic and mediastinal disorders		Haemoptysis Dyspnoea Cough[a] Oropharyngeal pain[a,e] Epistaxis	Acute respiratory distress syndrome[a] Respiratory failure[a] Pulmonary oedema[a] Interstitial lung disease[a] Lung infiltration[a] Pulmonary haemorrhage Hypoxia	
Gastrointestinal disorders	Diarrhoea[a,e] Vomiting[a,e] Nausea[a]	Constipation[e] Oral pain		
Hepatobiliary disorders		Blood alkaline phosphatase increased Hepatomegaly	Gamma-glutamyl transferase increased Aspartate aminotransferase increased	
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Rash maculopapular	Sweets syndrome (acute febrile neutrophilic dermatosis) Cutaneous vasculitis[a]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[c]	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Urine abnormality Glomerulonephritis
General disorders and administrat	Fatigue[a] Mucosal inflammation[a] Pyrexia	Chest pain[a] Asthenia[a] Pain[a] Malaise[e]	Injection site reaction	

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)
ion site conditions		Oedema peripheral[e]		
Injury, poisoning and procedural complications		Transfusion reaction[e]		

[a] See section c (Description of selected adverse reactions)
[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section c)
[c] Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain
[d] Cases were observed in the post-marketing setting in patient undergoing bone marrow transplant or PBPC mobilisation
[e] Adverse events with higher incidence in Filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy

c. Description of selected adverse reactions

GvHD
There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see sections 4.4 and 5.1).

Capillary leak syndrome
Cases of capillary leak syndrome have been reported with granulocyte-colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis (see section 4.4).

Sweets syndrome
Cases of Sweets syndrome (acute febrile neutrophilic dermatosis) have been reported in patients treated with filgrastim.

Pulmonary adverse events
In clinical studies and the post-marketing setting pulmonary adverse effects including interstitial lung disease, pulmonary oedema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4)

Splenomegaly and Splenic rupture
Cases of splenomegaly and splenic rupture have been reported following administration of filgrastim. Some cases of splenic rupture were fatal (see section 4.4).

Hypersensitivity
Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post-marketing experience. Overall, reports were more common after IV administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Cutaneous vasculitis

Cutaneous vasculitis has been reported in patients treated with Filgrastim. The mechanism of vasculitis in patients receiving Filgrastim is unknown. During long term use cutaneous vasculitis has been reported in 2% of SCN patients.

Pseudogout (chondrocalcinosis pyrophosphate)
Pseudogout (chondrocalcinosis pyrophosphate) has been reported in cancer patients treated with filgrastim.

Leukocytosis
Leukocytosis (WBC > 50 x 10^9/L) was observed in 41% of normal donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35% of donors (see section 4.4).

d. Paediatric population

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy suggesting no age-related differences in the pharmacokinetics of filgrastim. The only consistently reported adverse event was musculoskeletal pain which is no different from the experience in the adult population.

There is insufficient data to further evaluate filgrastim use in paediatric subjects.

e. Other special populations

Geriatric Use
No overall differences in safety or effectiveness were observed between subjects over 65 years of age compared to younger adult (>18 years of age) subjects receiving cytotoxic chemotherapy and clinical experience has not identified differences in the responses between elderly and younger adult patients. There is insufficient data to evaluate Accofil use in geriatric subjects for other approved Accofil indications.

Paediatric SCN patients
Cases of decreased bone density and osteoporosis have been reported in paediatric patients with severe chronic neutropenia receiving chronic treatment with filgrastim.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The effects of Accofil overdosage have not been established. Discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factors, ATC code: L03AA02
Accofil is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Accofil containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes. In some SCN patients, filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.

Use of filgrastim in patients undergoing cytotoxic chemotherapy leads to significant reductions in the incidence, severity and duration of neutropenia and febrile neutropenia. Treatment with filgrastim significantly reduces the duration of febrile neutropenia, antibiotic use and hospitalisation after induction chemotherapy for acute myelogenous leukaemia or myeloablative therapy followed by bone marrow transplantation. The incidence of fever and documented infections were not reduced in either setting. The duration of fever was not reduced in patients undergoing myeloablative therapy followed by bone marrow transplantation.

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into the peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

Recipients of allogeneic PBPCs mobilised with filgrastim experienced significantly more rapid haematological recovery, leading to a significant decrease in time to unsupported platelet recovery when compared with allogeneic bone marrow transplantation.

One retrospective European study evaluating the use of G-CSF after allogeneic bone marrow transplantation in patients with acute leukaemias suggested an increase in the risk of GvHD, treatment related mortality (TRM) and mortality when G-CSF was administered. In a separate retrospective international study in patients with acute and chronic myelogenous leukaemias, no effect on the risk of GvHD, TRM and mortality was seen. A meta-analysis of allogeneic transplant studies, including the results of nine prospective randomized trials, 8 retrospective studies and 1 case-controlled study, did not detect an effect on the risks of acute GvHD, chronic GvHD or early treatment-related mortality.

Relative risk (95% CI) of GvHD and TRM following treatment with G-CSF after bone marrow (BM) transplantation

Publication	**Period of Study**	**N**	**Acute Grade II - IV GvHD**	**Chronic GvHD**	**TRM**
Meta-Analysis (2003)	1986 - 2001[a]	1198	1.08 (0.87, 1.33)	1.02 (0.82, 1.26)	0.70 (0.38, 1.31)
European Retrospective Study (2004)	1992 - 2002[b]	1789	1.33 (1.08, 1.64)	1.29 (1.02, 1.61)	1.73 (1.30, 2.32)
International Retrospective Study (2006)	1995 - 2000[b]	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)

[a] Analysis includes studies involving BM transplant during this period; some studies used GM-CSF

[b] Analysis includes patients receiving BM transplant during this period

Use of filgrastim for the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

In normal donors, a 10 µg/kg/day dose administered subcutaneously for 4 - 5 consecutive days allows a collection of $\geq 4 \times 10^6$ $CD34^+$ cells/kg recipient body weight in the majority of the donors after two leukaphereses.

Use of filgrastim in patients, children or adults, with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in absolute neutrophil counts in peripheral blood and a reduction of infection and related events.

Use of filgrastim in patients with HIV infection maintains normal neutrophil counts to allow scheduled dosing of antiviral and/or other myelosuppressive medication. There is no evidence that patients with HIV infection treated with filgrastim show an increase in HIV replication.

As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/ml for 8 - 16 hours.

Distribution

The volume of distribution in blood is approximately 150 ml/kg.

Elimination

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The serum elimination half-life of filgrastim is approximately 3.5 hours, with a clearance rate of approximately 0.6 ml/min/kg. Continuous infusion with Accofil over a period of up to 28 days, in patients recovering from autologous bone-marrow transplantation, resulted in no evidence of drug accumulation and comparable elimination half-lives.

Linearity

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

5.3 Preclinical safety data

Filgrastim was studied in repeated dose toxicity studies up to 1 year in duration which revealed changes attributable to the expected pharmacological actions including increases in leucocytes , myeloid hyperplasia in bone marrow, extramedullary granulopoiesis and splenic enlargement. These changes all reversed after discontinuation of treatment.
Effects of filgrastim on prenatal development have been studied in rats and rabbits. Intravenous (80 µg/kg/day) administration of filgrastim to rabbits during the period of organogenesis was maternally toxic and increased spontaneous abortion, post-implantation loss, and decreased mean live litter size and foetal weight were observed.
Based on reported data for another filgrastim product similar to Accofil, comparable findings plus increased foetal malformations were observed at 100 µg/kg/day, a maternally toxic dose which corresponded to a systemic exposure of approximately 50-90 times the exposures observed in patients treated with the clinical dose of 5 µg/kg/day. The no observed adverse effect level for embryo-foetal

toxicity in this study was 10 µg/kg/day, which corresponded to a systemic exposure of approximately 3-5 times the exposures observed in patients treated with the clinical dose.
In pregnant rats, no maternal or foetal toxicity was observed at doses up to 575 µg/kg/day. Offspring of rats administered filgrastim during the peri-natal and lactation periods, exhibited a delay in external differentiation and growth retardation (≥20 µg/kg/day) and slightly reduced survival rate (100 µg/kg/day).
Filgrastim had no observed effect on the fertility of male or female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid glacial
Sodium hydroxide
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

Accofil must not be diluted with sodium chloride solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

This medicinal product must not be mixed with other products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

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

Within its shelf-life and for the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 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 syringe in the outer carton in order to protect from light.

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.

6.5 Nature and contents of container

Type I glass pre-filled syringe with a permanently attached stainless steel needle in the tip and 1/40 printed markings for graduations from 0.1 mL to 1 mL on the barrel. The needle cover of the pre-filled syringe contains dry natural rubber (see section 4.4). Each pre-filled syringe contains 0.73 ml solution.

Each pack contains one, three, five, seven or ten pre-filled syringes, with or without a needle safety guard, and alcohol swabs. The packs without blister are for syringes without needle safety guard. The blister packs are for individual syringes with prefixed needle safety guard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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. Do not shake.

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.

Accofil contains no preservative. In view of the possible risk of microbial contamination, Accofil pre-filled syringes are for single use only.

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

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.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/28
EU/1/14/946/29
EU/1/14/946/30
EU/1/14/946/31
EU/1/14/946/32
EU/1/14/946/33
EU/1/14/946/34
EU/1/14/946/35
EU/1/14/946/36

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 18.09.2014
Date of latest renewal: 12th June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)
Intas Pharmaceuticals Ltd.
Plot no: 423/P/A
Sarkhej Bavla Highway
Village Moraiya; Taluka Sanand,
Ahmedabad – 382213 Gujarat
India

Name and address of the manufacturer(s) responsible for batch release
Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

Accord Healthcare Single Member S.A.,
64th Km National Road Athens Lamia,Schimatari,
32009, Greece

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic safety update reports

The marketing authorisation holder shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

Accofil 30 MU/0.5 ml solution for injection/infusion
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe in 0.5 ml contains 30 MU of filgrastim (0.6 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injection. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe (0.5 ml) + 1 alcohol swab
"5 pre-filled syringes (0.5 ml) + 5 alcohol swabs"
"3 pre-filled syringe (0.5 ml) + 3 alcohol swabs"
"10 pre-filled syringe (0.5 ml) + 10 alcohol swabs"

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous or intravenous use.
Do not shake

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/001 - 1 prefilled syringe
EU/1/14/946/002 - 5 prefilled syringes
EU/1/14/946/006 - 3 prefilled syringe
EU/1/14/946/009 - 10 prefilled syringe

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Accofil 30 MU/0.5 ml

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton – Pre-filled syringe with a needle safety guard in blister pack

1. NAME OF THE MEDICINAL PRODUCT

Accofil 30 MU/0.5 ml solution for injection/infusion
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe in 0.5 ml contains 30 MU of filgrastim (0.6 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injection. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe (0.5 ml) + 1 alcohol swab
"3 pre-filled syringe (0.5 ml) + 3 alcohol swabs"
"5 pre-filled syringes (0.5 ml) + 5 alcohol swabs"
"10 pre-filled syringe (0.5 ml) + 10 alcohol swabs"
"7 pre-filled syringe (0.5 ml) + 7 alcohol swabs"

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous or intravenous use.
Do not shake

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/005 – 1 prefilled syringe with a needle safety guard
EU/1/14/946/008 – 5 prefilled syringes with a needle safety guard
EU/1/14/946/007 – 3 prefilled syringe with a needle safety guard
EU/1/14/946/010 – 10 prefilled syringe with a needle safety guard
EU/1/14/946/017 – 7 prefilled syringe with a needle safety guard

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Accofil 30 MU/0.5 ml

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Accofil 30 MU/0.5 ml solution for injection/infusion
filgrastim
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

Accofil 48 MU/0.5 ml solution for injection/infusion
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe in 0.5 ml contains 48 MU of filgrastim (0.96 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injection. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe (0.5 ml) + 1 alcohol swab
"5 pre-filled syringes (0.5 ml) + 5 alcohol swabs"
"3 pre-filled syringe (0.5 ml) + 3 alcohol swabs"
"10 pre-filled syringe (0.5 ml) + 10 alcohol swabs"

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous or intravenous use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/003 - 1 prefilled syringe
EU/1/14/946/004 - 5 prefilled syringes
EU/1/14/946/012 - 3 prefilled syringe
EU/1/14/946/015 - 10 prefilled syringe

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Accofil 48 MU/0.5 ml

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton – Pre-filled syringe with a needle safety guard in blister pack

1. NAME OF THE MEDICINAL PRODUCT

Accofil 48 MU/0.5 ml solution for injection/infusion
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe in 0.5 ml contains 48 MU of filgrastim (0.96 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injection. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe (0.5 ml) + 1 alcohol swab
"3 pre-filled syringe (0.5 ml) + 3 alcohol swabs"
"5 pre-filled syringes (0.5 ml) + 5 alcohol swabs"
"10 pre-filled syringe (0.5 ml) + 10 alcohol swabs"
"7 pre-filled syringe (0.5 ml) + 7 alcohol swabs"

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous or intravenous use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/011 – 1 prefilled syringe with a needle safety guard
EU/1/14/946/014 – 5 prefilled syringes with a needle safety guard
EU/1/14/946/013 – 3 prefilled syringe with a needle safety guard
EU/1/14/946/016 – 10 prefilled syringe with a needle safety guard
EU/1/14/946/018 – 7 prefilled syringe with a needle safety guard

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Accofil 48 MU/0.5 ml

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Accofil 48 MU/0.5 ml solution for injection/infusion
filgrastim

SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

Accofil 12 MU/0.2 mL solution for injection/infusion
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe in 0.2 ml contains 12 MU of filgrastim (0.6 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injection. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe (0.2 ml) + 1 alcohol swab
"5 pre-filled syringes (0.2 ml) + 5 alcohol swabs"
"3 pre-filled syringe (0.2 ml) + 3 alcohol swabs"
"10 pre-filled syringe (0.2 ml) + 10 alcohol swabs"

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous or intravenous use.
Do not shake

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/019 – 1 prefilled syringe
EU/1/14/946/020 – 3 prefilled syringes
EU/1/14/946/021 – 5 prefilled syringe
EU/1/14/946/022 – 10 prefilled syringe

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Accofil 12 MU/0.2 mL

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton – Pre-filled syringe with a needle safety guard in blister pack

1. NAME OF THE MEDICINAL PRODUCT

Accofil 12 MU/0.2 mL solution for injection/infusion
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe in 0.2 ml contains 12 MU of filgrastim (0.6 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injection. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe (0.2 ml) + 1 alcohol swab
"3 pre-filled syringe (0.2 ml) + 3 alcohol swabs"
"5 pre-filled syringes (0.2 ml) + 5 alcohol swabs"
"10 pre-filled syringe (0.2 ml) + 10 alcohol swabs"
"7 pre-filled syringe (0.2 ml) + 7 alcohol swabs"

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous or intravenous use.
Do not shake

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/023 – 1 prefilled syringe with a needle safety guard
EU/1/14/946/024 – 3 prefilled syringes with a needle safety guard
EU/1/14/946/025 – 5 prefilled syringe with a needle safety guard
EU/1/14/946/026 – 7 prefilled syringe with a needle safety guard
EU/1/14/946/027 – 10 prefilled syringe with a needle safety guard

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Accofil 12 MU/0.2 mL

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Accofil 12 MU/0.2 mL solution for injection/infusion
filgrastim
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

Accofil 70 MU/0.73 ml solution for injection/infusion
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe in 0.73 ml contains 70 MU of filgrastim (0.96 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injection. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe (0.73 ml) + 1 alcohol swab
"5 pre-filled syringes (0.73 ml) + 5 alcohol swabs"
"3 pre-filled syringe (0.73 ml) + 3 alcohol swabs"
"10 pre-filled syringe (0.73 ml) + 10 alcohol swabs"

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous or intravenous use.
Do not shake

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/028 – 1 prefilled syringe
EU/1/14/946/029 – 3 prefilled syringes
EU/1/14/946/030 – 5 prefilled syringe
EU/1/14/946/031 – 10 prefilled syringe

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Accofil 70 MU/0.73 ml

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton – Pre-filled syringe with a needle safety guard in blister pack

1. NAME OF THE MEDICINAL PRODUCT

Accofil 70 MU/0.73 ml solution for injection/infusion
filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each syringe in 0.73 ml contains 70 MU of filgrastim (0.96 mg/ml).

3. LIST OF EXCIPIENTS

Acetic acid, sodium hydroxide, sorbitol (E420), polysorbate 80, and water for injection. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe (0.73 ml) + 1 alcohol swab
"3 pre-filled syringe (0.73 ml) + 3 alcohol swabs"
"5 pre-filled syringes (0.73 ml) + 5 alcohol swabs"
"10 pre-filled syringe (0.73 ml) + 10 alcohol swabs"
"7 pre-filled syringe (0.73 ml) + 7 alcohol swabs"

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Subcutaneous or intravenous use.
Do not shake

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/946/032 – 1 prefilled syringe with a needle safety guard
EU/1/14/946/033 – 3 prefilled syringes with a needle safety guard
EU/1/14/946/034 – 5 prefilled syringe with a needle safety guard
EU/1/14/946/035 – 7 prefilled syringe with a needle safety guard
EU/1/14/946/036 – 10 prefilled syringe with a needle safety guard

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Accofil 70 MU/0.73 ml

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Accofil 70 MU/0.73 ml solution for injection/infusion
filgrastim
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.73 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Accofil 30 MU/0.5 ml (0.6 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

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;
- 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 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

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, nurse 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.

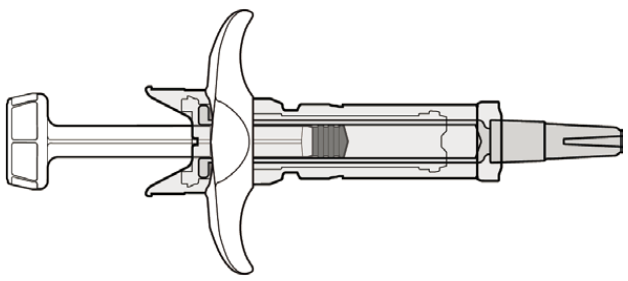
Equipment that you need
To give yourself a subcutaneous injection you will need:
- a pre-filled syringe of Accofil;
- alcohol swab or similar.

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.
a. Take your Accofil pre-filled syringe out of the refrigerator.
b. 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.
c. 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
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.

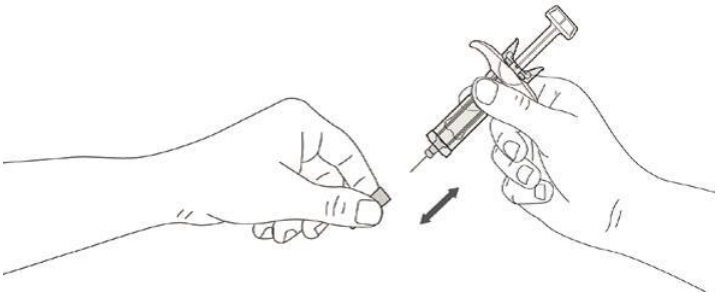
Picture 1



Step 2: Remove the Needle Cap

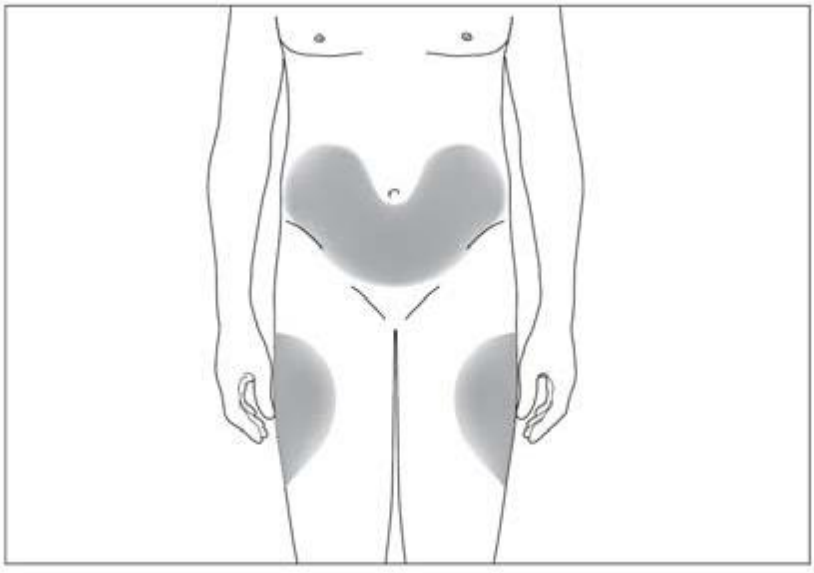
a. Remove the protective cap as shown in picture 2. Hold the body of the needle safety guard in one hand with the needle end pointing away from you and without touching the plunge rod. Pull the needle cap straight off with your other hand. After removal, throw away the needles cap in a biohazard (sharps) container.
b. 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.
c. 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.
d. Check again to make sure the correct dose of Accofil is in the syringe.
e. You can now use the pre-filled syringe.

Picture 2



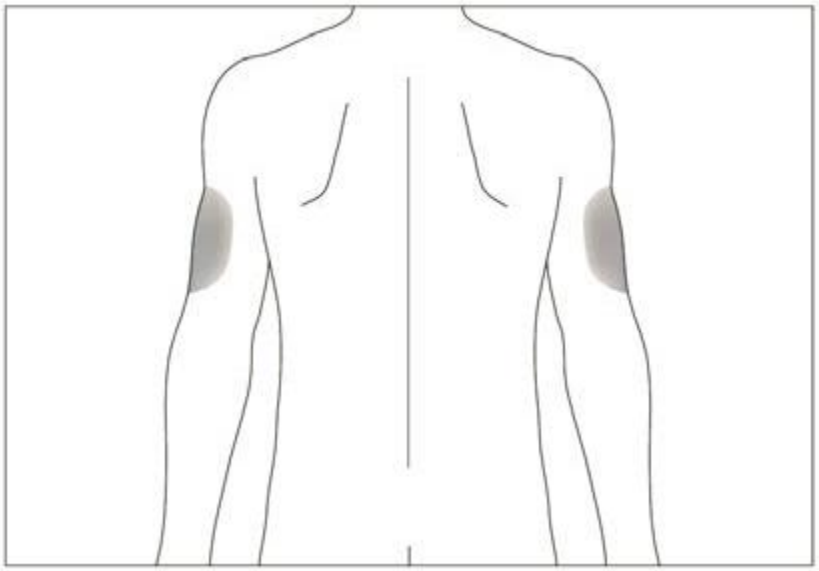
Where should I give my injection?
The most suitable places to inject yourself are:
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).

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.

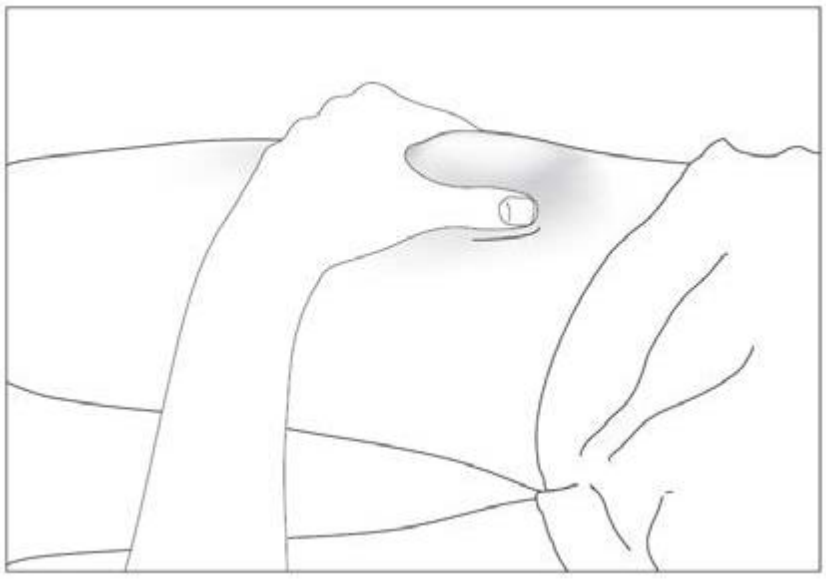
Step 3: Insert the Needle

- 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

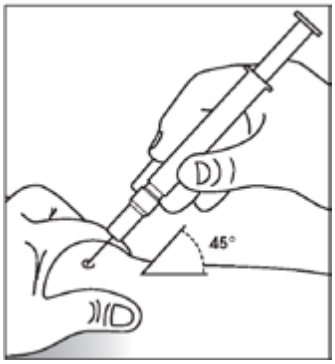


<u>Pre-filled syringe without needle safety guard</u>

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

- 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.
- Inject only the dose your doctor has told you.
- After injecting the liquid, remove the needle while maintaining pressure on the plunger and then let go of your skin.
- Put the used syringe in the disposal container. Use each syringe only for one injection.

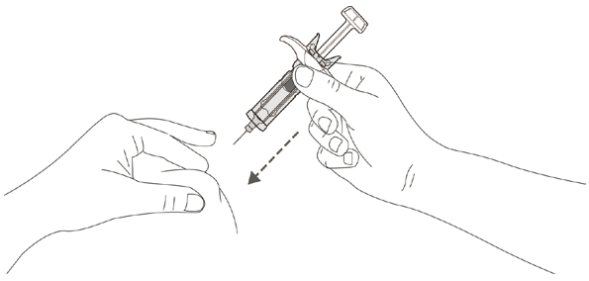
Picture 6



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.
3. Inject only the dose your doctor has told you following the instructions below.

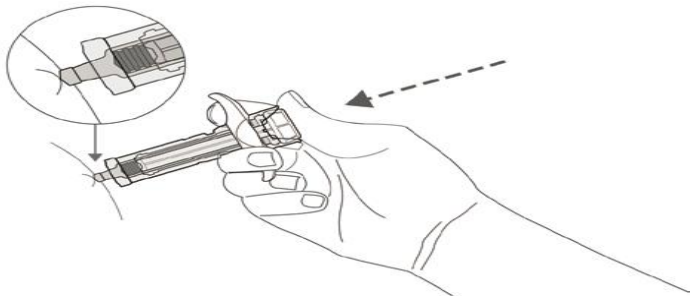
Picture 7



Step-4: Injection

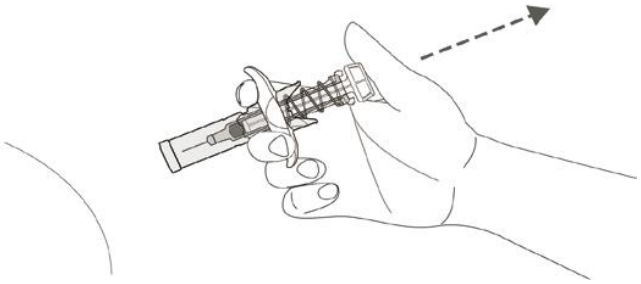
Place the thumb on the plunger rod head. Depress the plunger rod and **push firmly** at the end of the injection to ensure that syringe emptying is completed (see picture 8). Hold the skin securely until the injection is completed.

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 injectedmore 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 doses.

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
- formation of blood cells outside of the bone marrow (extramedullary haematopoiesis).

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 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.

Marketing Authorisation Holder
Accord Healthcare S.L.U.

World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

Manufacturer
Accord Healthcare Polska Sp.z o.o.,
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Accord Healthcare Single Member S.A.,
64th Km National Road Athens Lamia,Schimatari,
32009, Greece

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

AT / BE / BG / CY / CZ / DE / DK / EE / FI / FR / HR / HU / IE / IS / IT / LT / LV / LU / MT / NL / NO / PT / PL / RO / SE / SI / SK / ES
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://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.

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 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.

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

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;
.
- 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.

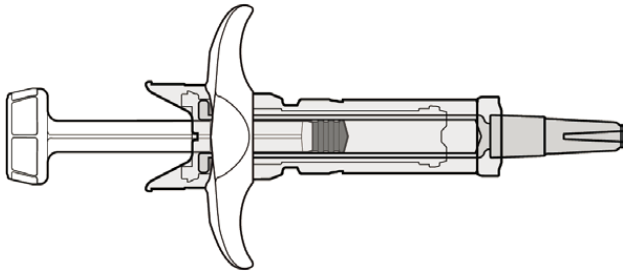
Equipment that you need
To give yourself a subcutaneous injection you will need:
- a pre-filled syringe of Accofil;
- alcohol swab or similar.

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

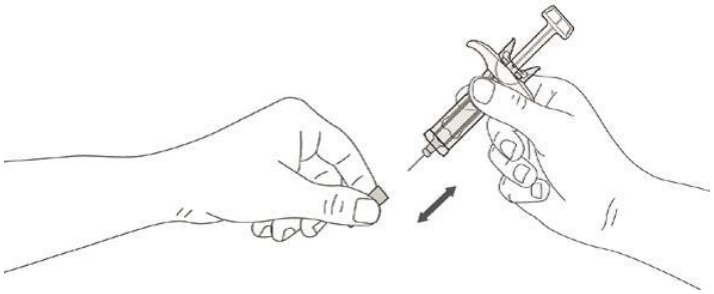
Picture 1



Step 2: Remove the Needle Cap

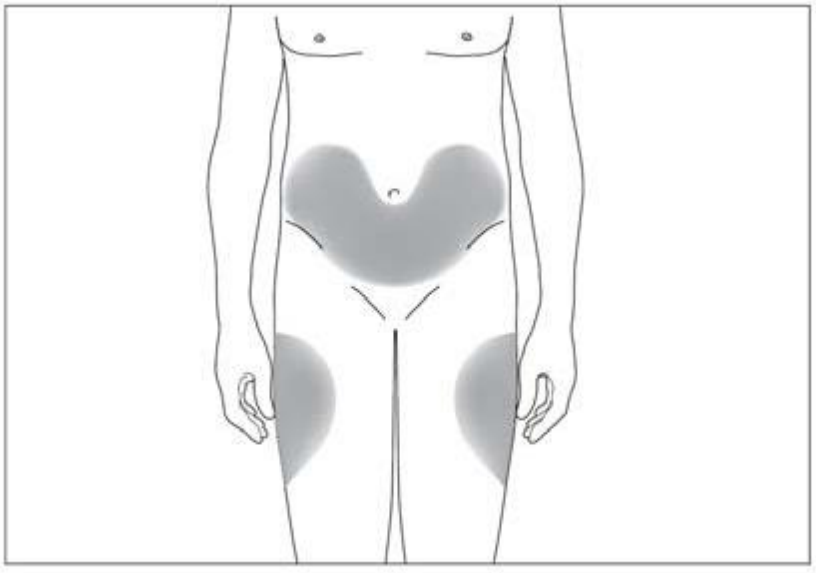
1. Remove the protective cap as shown in picture 2. Hold the body of the needle safety guard in one hand with the needle end pointing away from you and without touching the plunge rod. Pull the needle cap straight off with your other hand. After removal, throw away the needles cap in a biohazard (sharps) 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



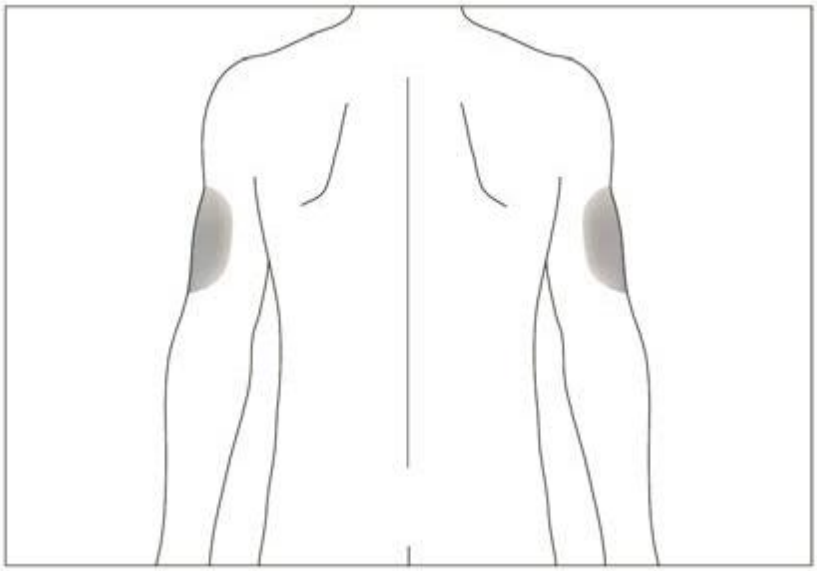
Where should I give my injection?
The most suitable places to inject yourself are:
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).

Picture 3



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

Picture 4



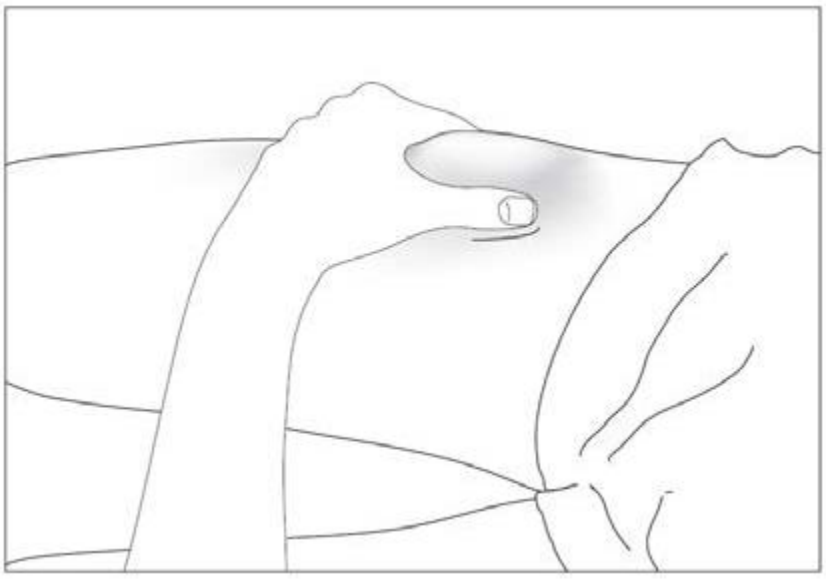
It is better to change the injection site every day to avoid the risk of soreness at any one site.

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

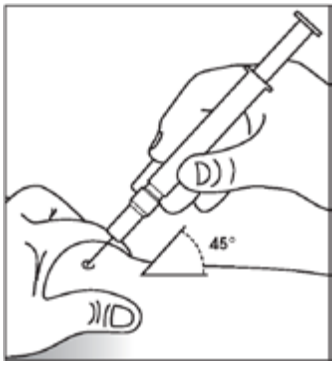


Pre-filled syringe without needle safety guard

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.

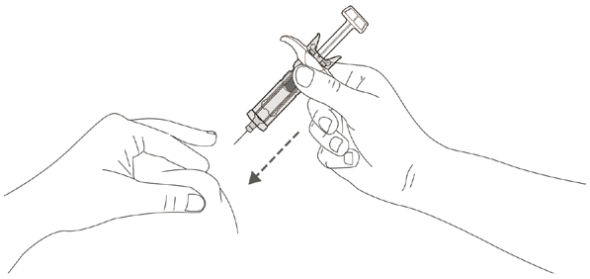
Picture 6



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.

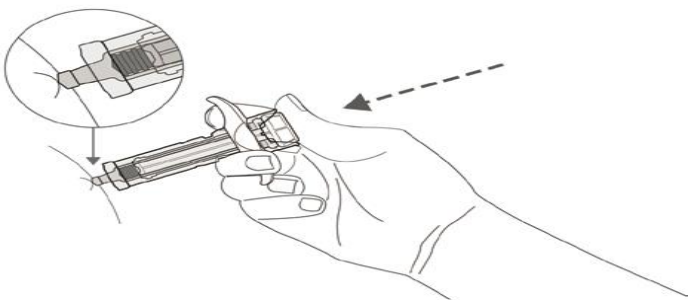
Picture 7



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

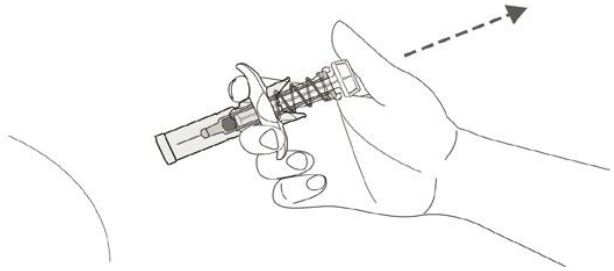
Picture 8



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
- formation of blood cells outside of the bone marrow (extramedullary haematopoiesis).

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
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

Manufacturer
Accord Healthcare Polska Sp.z o.o.,

ul. Lutomierska 50, 95-200 Pabianice, Poland

Accord Healthcare Single Member S.A.,
64th Km National Road Athens Lamia,Schimatari,
32009, Greece

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

AT / BE / BG / CY / CZ / DE / DK / EE / FI / FR / HR / HU / IE / IS / IT / LT / LV / LU / MT / NL / NO / PT / PL / RO / SE / SI / SK / ES
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EL
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://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.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Accofil 12 MU/0.2 ml (0.6 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

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;
- 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, nurse 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.

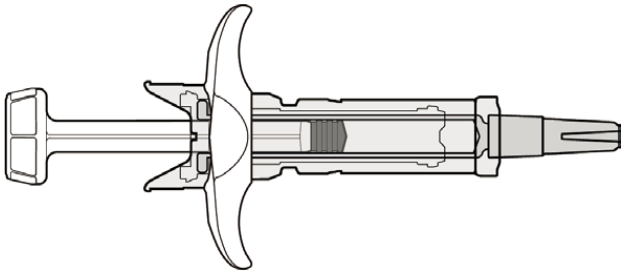
Equipment that you need
To give yourself a subcutaneous injection you will need:
- a pre-filled syringe of Accofil;
- alcohol swab or similar.

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.
a. Take your Accofil pre-filled syringe out of the refrigerator.
b. 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.
c. 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
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.

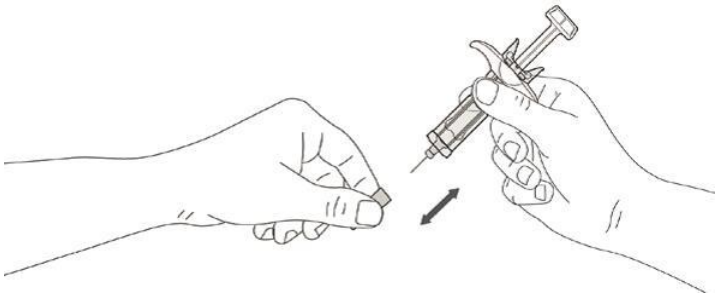
Picture 1



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.

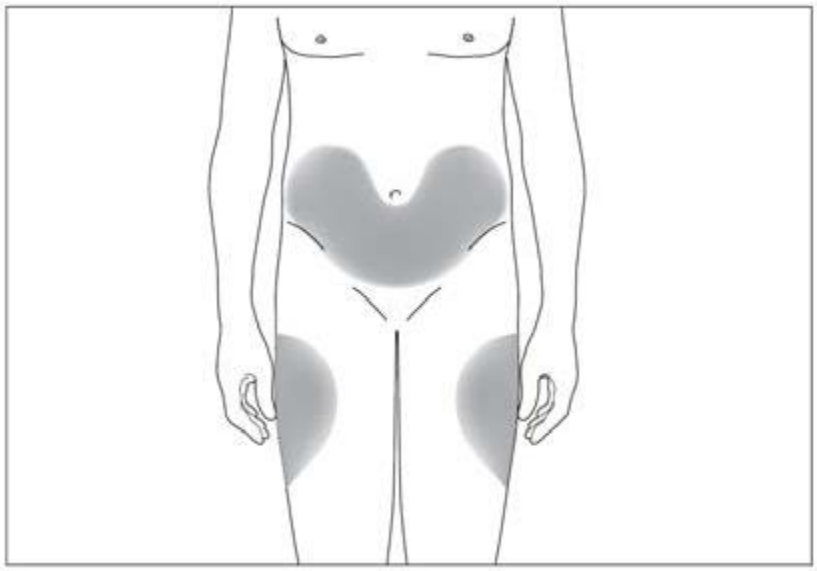
Picture 2.



Where should I give my injection?
The most suitable places to inject yourself are:

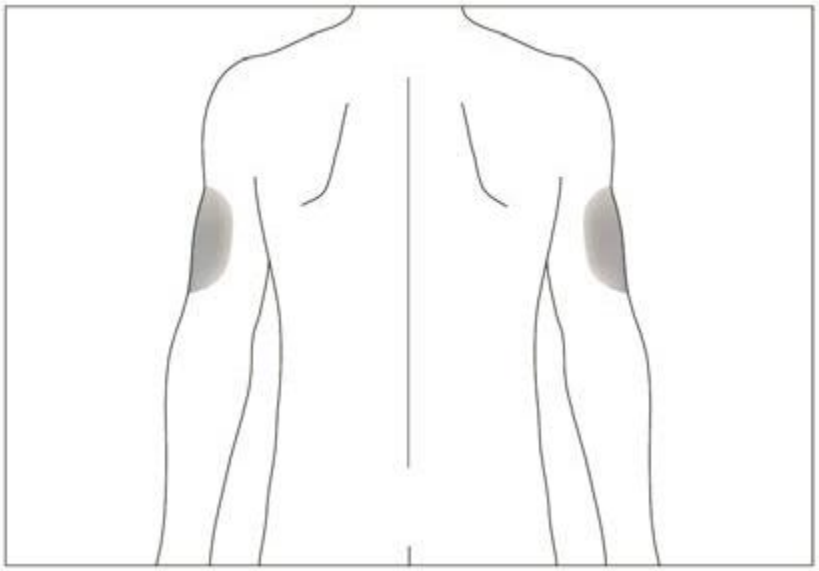
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).

Picture 3.



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

Picture 4.



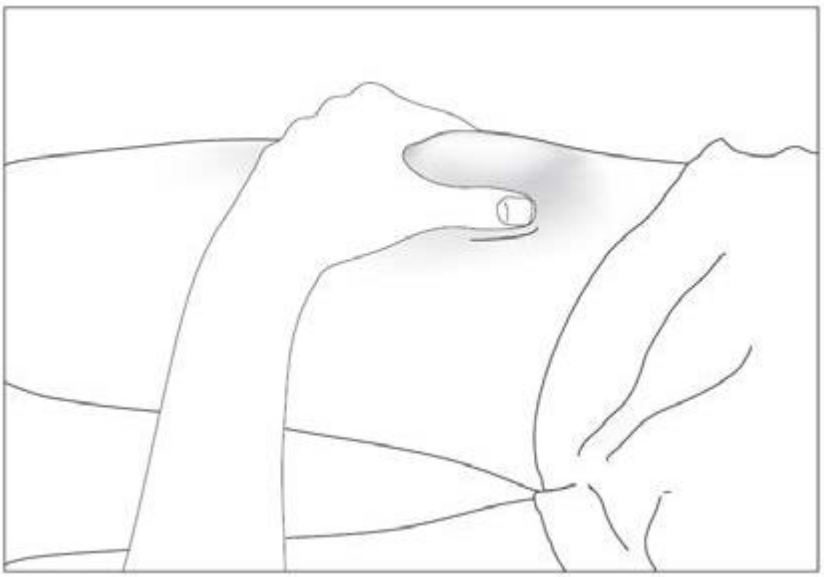
It is better to change the injection site every day to avoid the risk of soreness at any one site.

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.

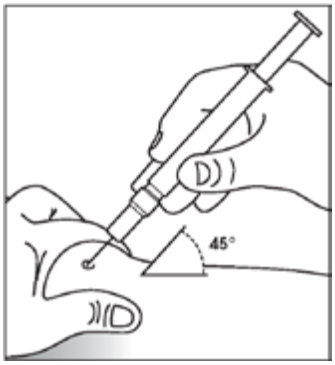


Pre-filled syringe without needle safety guard

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.

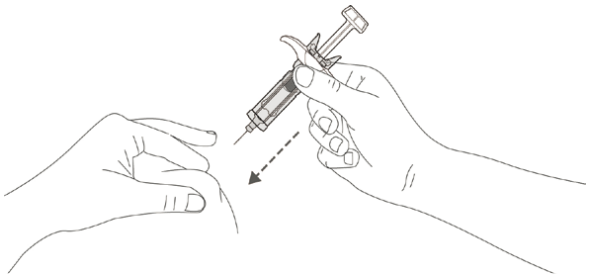
Picture 6.



Pre-filled syringe with needle safety guard

- Put the needle fully into the skin as shown by your nurse or doctor
- 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.

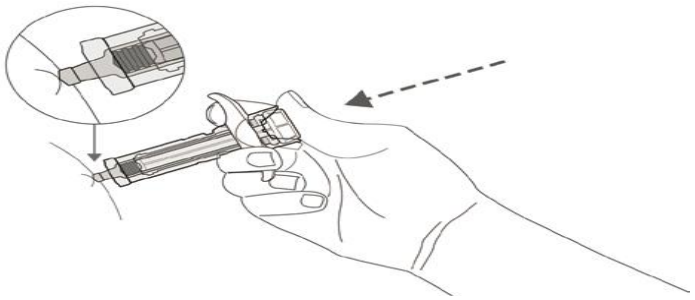
Picture 7.



Step-4: Injection

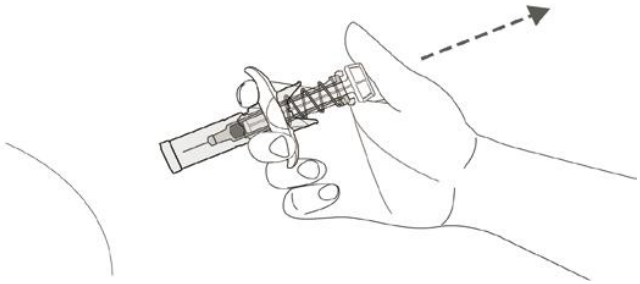
Place the thumb on the plunger rod head. Depress the plunger rod and **push firmly** at the end of the injection to ensure that syringe emptying is completed (see picture 8). Hold the skin securely until the injection is completed.

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
- formation of blood cells outside of the bone marrow (extramedullary haematopoiesis).

Reporting of side effects

If you get any side effects, talk to your doctor ornurse. 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 12 MU (120 micrograms) filgrastim in 0.2 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 0.2 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
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

Manufacturer
Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

Accord Healthcare Single Member S.A.,
64th Km National Road Athens Lamia,Schimatari,
32009, Greece

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

AT / BE / BG / CY / CZ / DE / DK / EE / FI / FR / HR / HU / IE / IS / IT / LT / LV / LU / MT / NL / NO / PT / PL / RO / SE / SI / SK / ES
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Win Medica A.E.
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://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.

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 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.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Accofil 70 MU/0.73 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

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;
- 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, 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.

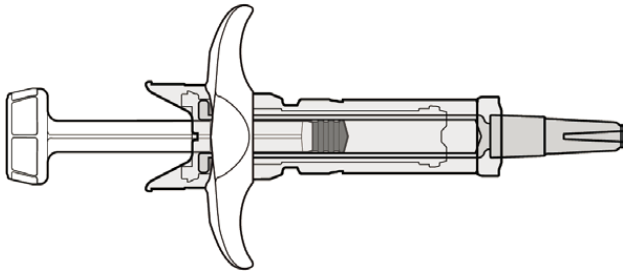
Equipment that you need
To give yourself a subcutaneous injection you will need:
- a pre-filled syringe of Accofil;
- alcohol swab or similar.

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.
a. Take your Accofil pre-filled syringe out of the refrigerator.
b. 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.
c. 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
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

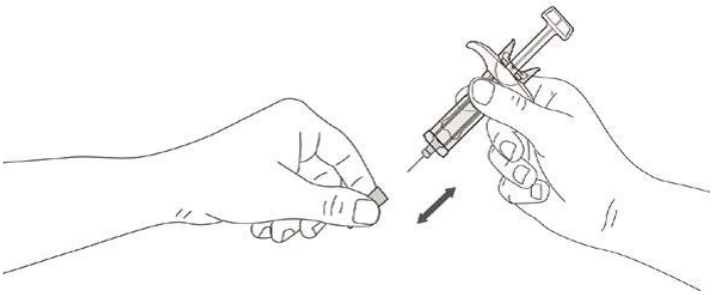
Picture 1.



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.

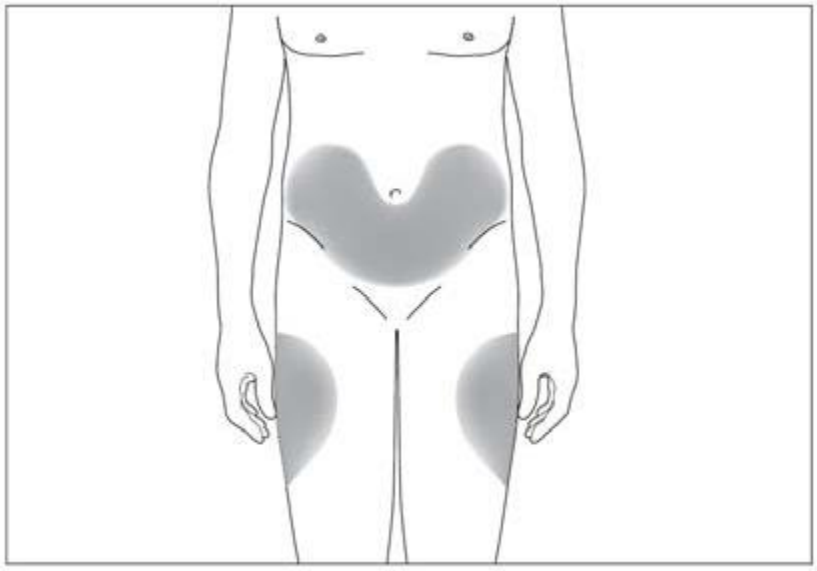
Picture 2.



Where should I give my injection?
The most suitable places to inject yourself are:

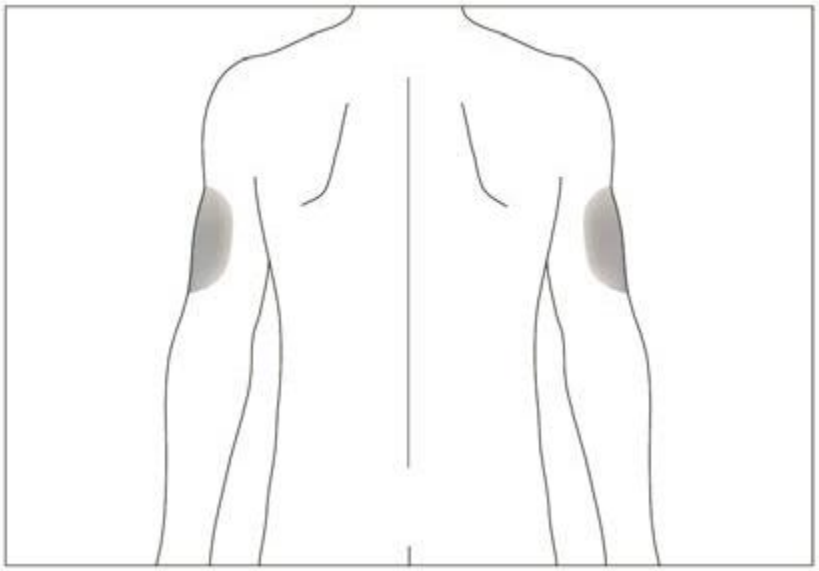
- the top of your thighs; and
- the abdomen, except for the area around the navel (see picture 3).

Picture 3.



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

Picture 4.



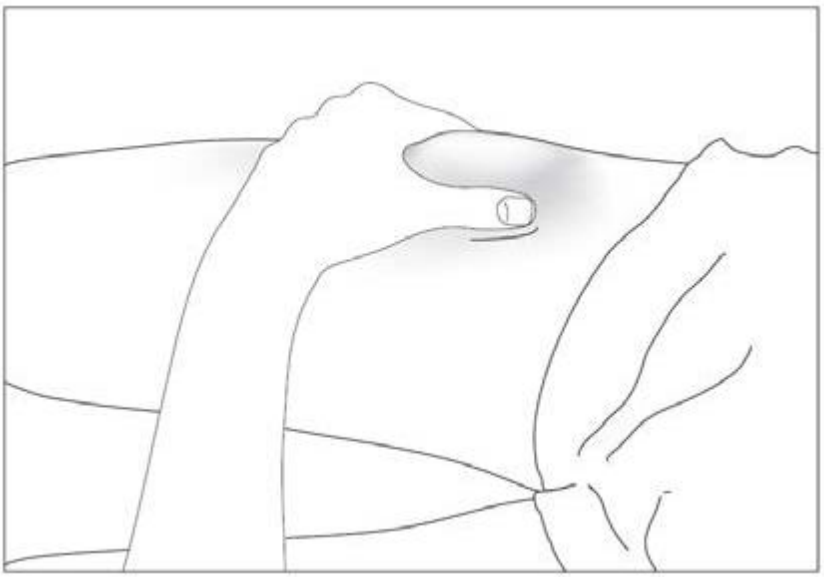
It is better to change the injection site every day to avoid the risk of soreness at any one site.

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

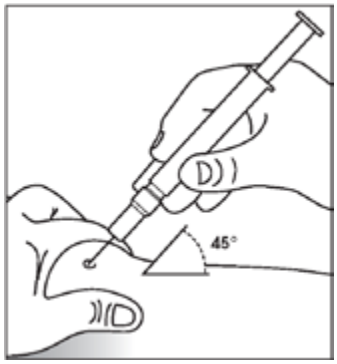


Pre-filled syringe without needle safety guard

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.

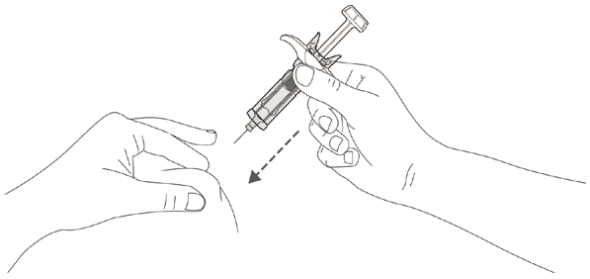
Picture 6.



Pre-filled syringe with needle safety guard

- Put the needle fully into the skin as shown by your nurse or doctor
- 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.

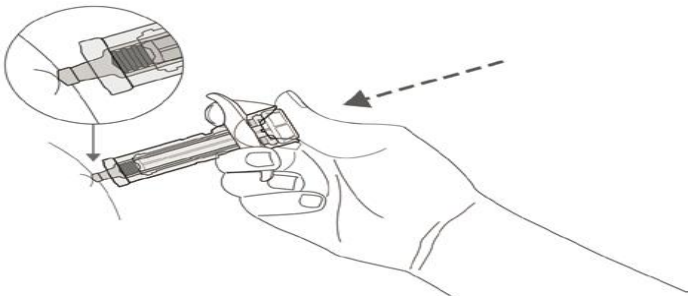
Picture 7.



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

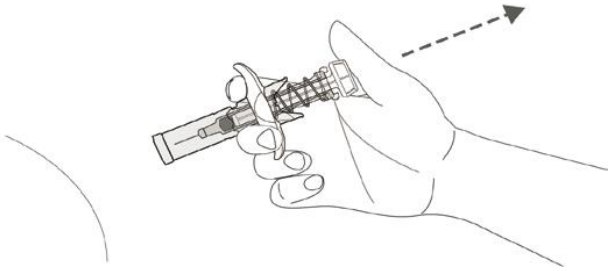
Picture 8.



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 or pharmacist 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 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 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
- formation of blood cells outside of the bone marrow (extramedullary haematopoiesis).

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 70 MU (700 micrograms) filgrastim in 0.73 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 0.73 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
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
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Spain

Manufacturer
Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

Accord Healthcare Single Member S.A.,
64th Km National Road Athens Lamia,Schimatari,
32009, Greece

For any information about this medicine, please contact the local representative of the 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: https://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.

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 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.