Package Insert

ACCOFIL
Solution for Injection or Infusion in Pre-filled Syringe 48 MU/0.5 mL and 30 MU/0.5 mL

1. NAME OF THE MEDICINAL PRODUCT

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

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Accofil 48 MU/0.5 ml
Each ml of solution contains 96 million units (MU) (equivalent to 960 micrograms [µg]) of filgrastim.

Each pre-filled syringe contains 48 MU (equivalent to 480 micrograms of filgrastim in 0.5 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.

Accofil 30 MU/0.5 ml
Each ml of solution contains 60 million units (MU) (equivalent to 600 micrograms [µg]) of filgrastim.

Each pre-filled syringe contains 30 MU (equivalent to 300 micrograms of filgrastim in 0.5 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 infusion

Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Established cytotoxic chemotherapy
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 and its clinical sequelae in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

Peripheral blood progenitor cell mobilisation (PBPC)
Accofil is indicated for the mobilisation of autologous peripheral blood progenitor cells (PBPC) alone, or following myelosuppressive chemotherapy and the mobilisation of peripheral blood progenitor cells in normal donors (allogeneic PBPC).

Severe chronic neutropenia (SCN)
Long-term administration of Neupogen is indicated in patients, children or adults, with severe congenital, cyclic or idiopathic neutropenia with an Absolute Neutrophil Count (ANC) $\leq 0.5 \times 10^9$/l, and a history of severe or recurrent infections, to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

HIV infection
Accofil is indicated for the treatment of persistent neutropenia (ANC $\leq 1.0 \times 10^9$/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/kg/day (5 micrograms/kg/day). The first dose of Accofil should not be administered less than 24 hours following cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 microgram/m^2/day (4.0 to 8.4 microgram/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 leukaemias, 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/kg/day (10 micrograms/kg/day). The first dose of filgrastim should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

The efficacy and safety of filgrastim given for longer than 28 days in this setting have not been established.

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

Absolute Neutrophil Count (ANC)	**Filgrastim dose adjustment**
ANC > 1.0 x 10^9/L for 3 consecutive days	Reduce to 0.5 MU/kg/day (5 micrograms/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	

Mobilisation of peripheral blood progenitor cells (PBPC)

Mobilisation of Peripheral Blood Progenitor Cells (PBPC) in patients undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell transplantation with or without bone marrow transplantation

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU/kg/day (10 micrograms/kg/day) as a 24 hour subcutaneous continuous infusion or a single daily subcutaneous injection for 5-7 consecutive days. The timing of leukapheresis: 1 or 2 leukaphereses on days 5 and 6 which is often sufficient. In other circumstances, additional leukaphereses 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/kg/day (5 micrograms/kg/day) given daily by subcutaneous injection 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 leukaphereses are recommended.

Mobilisation of Peripheral Blood Progenitor Cells (PBPC) in normal donors prior to allogeneic peripheral blood progenitor cell transplantation

For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU kg/day (10 micrograms/kg/day) subcutaneously for 4 - 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.

Severe chronic neutropenia (SCN)

Congenital neutropenia

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

Idiopathic or cyclic neutropenia

The recommended starting dose is 0.5 MU/kg/day (5 micrograms/kg/day) subcutaneously 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 1-2 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 studies, 97% of patients who responded had a complete response at doses of ≤ 2.4 MU/kg/day (24 micrograms/kg/day).

The long- term safety of administration of filgrastim at doses above 2.4 MU/kg/day (24 micrograms/kg/day) in patients with SCN has not been established.

HIV infection

For reversal of neutropenia

The recommended starting dose of filgrastim is 0.1 MU/kg/day (1 micrograms/kg/day) given daily by subcutaneous injection with titration up to a maximum of 0.4 MU/kg/day (4 micrograms/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 a reversal of neutropenia in a median of 2 days.

In a small number of patients (< 10%), doses up to 1.0 MU/kg/day (10 micrograms/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/day (300 micrograms/day) by subcutaneous injection 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/day (300 micrograms/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.

For Maintaining 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 micrograms)/day by subcutaneous injection 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 micrograms)/day on 1 to 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 patients

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 posology recommendations cannot be made.

Patients with renal/hepatic 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 patients in established cytotoxic chemotherapy

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

In patients undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell transplantation

The safety and efficacy of filgrastim have not been assessed in normal donors < 16 years.

Paediatric patients with severe chronic neutropenia (SCN)

The safety and efficacy in neonates have not been established.

Long term administration of filgrastim is indicated in children with severe congenital, cyclic or idiopathic neutropenia with an Absolute Neutrophil Count (ANC) $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Paediatric patients in the SCN and cancer settings

Sixty-five percent of patients studied in a SCN trial program with filgrastim administration, were under 18 years of age. The efficacy of the 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.

Method of administration

Established cytotoxic chemotherapy

Filgrastim may be administered as a daily subcutaneous injection or alternatively as a daily intravenous infusion diluted in glucose 50 mg/ml (5%) solution over 30 minutes. For further instructions on dilution prior to infusion 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 randomised clinical studies, a subcutaneous dose of 23 MU/m^2/day (230 micrograms/m^2/day) or rather 4-8.4 micrograms/kg/day was used.

Patients treated with myeloablative therapy followed by bone marrow transplantation

Filgrastim is administered as an intravenous short-term infusion over 30 minutes or as a subcutaneous or intravenous continuous infusion over 24 hours, in each case after dilution in 20 ml of glucose 50 mg/ml (5%) solution. For further instructions on dilution with glucose 50 mg/ml (5%) solution prior to infusion see section 6.6.

In patients with Mobilisation of PBPC

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 SCN

Congenital, idiopathic or cyclic neutropenia; filgrastim should be given by subcutaneous injection.

In patients with HIV infection

For the reversal of neutropenia and maintenance of normal neutrophil counts in patients with HIV infection, filgrastim is administered subcutaneously.

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

Special warnings

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

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

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.

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 GCSF.

Special precautions in patients with acute myeloid leukaemia (AML)

Malignant cell growth

G-CSF can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non- myeloid cells *in vitro*.

The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukaemia have not been established. Therefore, 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.

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.

Other special precautions

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.

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary 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 Adult Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given in these cases.

Capillary leak syndrome has been reported after granulocyte colony-stimulating factor administration, and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. 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).

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.

Special precautions in cancer patients

Cases of splenomegaly and splenic rupture have been reported uncommonly following administration of filgrastim. Some cases of splenic rupture were fatal. Individuals receiving filgrastim who report left upper abdominal and/ or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Leukocytosis

White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5% of 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. However, during the period of administration of filgrastim for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

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).

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.

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 mobilization

Mobilization of PBPC

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 optimal 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 (2.0×10^6 $CD34^+$ 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 peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilization 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 therefore, 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 yield of ≥ 2.0 x 10^6 $CD34^+$ cells/kg is based on published experience resulting in adequate haematologic reconstitution. Yields in excess of this minimum yield appear to correlate with more rapid recovery; those below with slower recovery.

Special precautions in normal donors undergoing peripheral blood progenitor cell mobilization

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. Particular attention should be paid 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 of age.

Thrombocytopenia has been reported very commonly in patients receiving filgrastim. Platelet counts should therefore be monitored closely.

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. Filgrastim administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L. Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.

Transient cytogenetic abnormalities have been observed in normal donors following G-CSF use. The significance of these changes is unknown. Nevertheless, a risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors for at least 10 years to ensure monitoring of long-term safety.

Common but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture have been reported in healthy donors and patients following administration of G-CSFs. 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 pain or shoulder tip pain.

In normal donors, dyspnoea has been reported commonly and other pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltrates, and hypoxia) have been reported uncommonly. In case of suspected or confirmed pulmonary adverse events, discontinuation of treatment with filgrastim should be considered and appropriate medical care given.

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

Blood cell counts

Thrombocytopenia has been reported commonly in patients receiving filgrastim. Platelet counts should be monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to intermittent cessation or decreasing the dose of filgrastim in patients who develop thrombocytopenia, i.e. platelets consistently < 100,000/mm^3. 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 was subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. If patients with SCN develop abnormal cytogenetics, the risks and benefits of continuing filgrastim should be carefully weighed; filgrastim should be discontinued if MDS or leukaemia occurs. 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.

Cases of splenomegaly have been reported very commonly and cases of splenic rupture have been reported commonly following administration of filgrastim. Individuals receiving filgrastim who report left upper abdominal and/ or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Splenomegaly is a direct effect of treatment with filgrastim. Thirty-one percent (31%) of patients in studies were documented as having palpable splenomegaly. Increases in volume, measured radiographically occurred early during filgrastim therapy and tended to plateau later in treatment. Dose reductions were noted to slow or stop the progression of splenic enlargement and in 3% of patients a splenectomy was required. Spleen size should be evaluated regularly. Abdominal palpation should be sufficient to detect abnormal increases in splenic volume.

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

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

<u>Special precautions in patients with HIV infection</u>

Cases of splenomegaly have been reported commonly following administration of filgrastim. Individuals receiving filgrastim who report left upper abdominal and/ or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Blood cell counts

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 weekly 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 microgram)/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.

Special precautions in sickle cell disease

Sickle cells crises, in some cases fatal, have been reported with the use of filgrastim in subjects with sickle cell disease. Physicians should exercise caution when considering the use of filgrastim in patients with sickle cell disease and only after careful evaluation of the potential risks and benefits.

All patients

Accofil contains sorbitol (E420) as an excipient at a concentration of 50 mg/ml. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product.

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

In order to improve the traceability of granulocyte-colony stimulating factors (G-CSFs), the trade name of the administered product should be clearly recorded in the patient file.

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, it 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

The safety of filgrastim has not been established in pregnant women. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. Studies in animals have shown reproductive toxicity. In pregnancy, the possible risk of filgrastim use to the fetus must be weighed against the expected therapeutic benefit.

Breast-feeding

It is not known whether filgrastim is excreted in human milk. Neupogen is not recommended for use in nursing women.

Fertility

Filgrastim had no observed effect on the fertility of male or female rats, or gestation, at doses up to 500 micrograms/kg.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials on cancer patients treated with filgrastim, the most frequent undesirable effect was musculoskeletal pain which was mild or moderate in 10% and in 3% of patients respectively.

Graft versus Host Disease (GvHD) has also been reported.

In PBPC mobilization in normal donors the most commonly reported undesirable effect was musculoskeletal pain. Leukocytosis was observed in donors and thrombocytopenia following filgrastim and leukapheresis was also observed in donors. Splenomegaly and splenic rupture were also reported. Some cases of splenic rupture were fatal.

In SCN patients the most frequent undesirable effects attributable to filgrastim were bone pain, general musculoskeletal pain and splenomegaly. Myelodysplastic syndromes (MDS) or leukaemia have developed in patients with congenital neutropenia treated with filgrastim (see section 4.4).

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly ($\geq$ 1/1000 to < 1/100) in cancer patients undergoing chemotherapy and healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony-stimulating factors (see section 4.4 and section 4.8).

In clinical studies with filgrastim administration to HIV patients, the only adverse effects consistently considered to be related to filgrastim administration were musculoskeletal pain, bone pain and myalgia.

Tabulated summary of adverse reactions

The data in the tables below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping undesirable effects are presented in order of decreasing seriousness. Data are presented separately for cancer patients, PBPC mobilisation in normal donors, SCN patients and patients with HIV, reflecting the different adverse reaction profiles in these populations.

The assessment of undesirable effects is based on the following frequency data:

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 Very rare: < 1/10,000
Not known: cannot be estimated from the available data.

Cancer patients

MedDRA system organ class	**Adverse reactions**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Blood and lymphatic system disorders			Sickle cell crisis[a] Spenomegaly Splenic rupture		
Immune system disorders		Drug hypersensitivity[a]	Graft versus Host Disease[b]		
Metabolism and nutrition disorders	Blood uric acid increased Blood lactate dehydrogenase increased Decreased appetite[a]		Pseudogout[b]		
Nervous system disorders	Headache[a]				
Vascular Disorders		Hypotension	Veno-occlusive disease[d] Fluid volume disturbances Capillary leak syndrome[a]		
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain[a] Cough[a] Dyspnoea	Haemoptysis[e]	Acute respiratory distress syndrome[a] Respiratory failure[a] Pulmonary oedema[a] Interstitial lung disease[a] Lung infiltration[a] Pulmonary haemorrhage		

Gastrointestinal disorders	Diarrhoea[a] Vomiting[a] Constipation[a]				

MedDRA system organ class	**Adverse reactions**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
	Nausea[a]				
Hepatobiliary disorders	Gamma-glutamyl transferase increased Blood alkaline phosphatase increased				
Skin and subcutaneous tissue disorders	Rash[a] Alopecia[a]		Sweets syndrome Cutaneous vasculitis[a]		
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[c]		Exacerbation of rheumatoid arthritis		
Renal and urinary disorders		Dysuria	Urine abnormality Glomerulonephritis		
General disorders and administration site conditions	Asthenia[a] Fatigue[a] Mucosal inflammation[a]	Chest pain[a]	Pain[a]		

[a] See section 4.8, Description of selected adverse reactions

[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section 4.8, Description of selected adverse reactions)

[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 with filgrastim in patients undergoing bone marrow transplant or PBPC mobilization

[e] Cases were observed in the clinical trial setting with filgrastim

PBPC mobilisation in normal donors

MedDRA system organ class	**Adverse reactions**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**

Blood and lymphatic system disorders	Thrombocytopenia Leukocytosis	Splenomegaly[a]	Splenic rupture Sickle cell crisis[a]		
Immune system disorders			Anaphylactic reaction		
Metabolism and nutrition disorders		Blood lactate dehydrogenase increased	Hyperuricaemia (blood uric acid increased)		
Nervous system disorders	Headache				

MedDRA system organ class	**Adverse reactions**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Vascular disorders			Capillary leak syndrome[a]		
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Pulmonary haemorrhage Haemoptysis Lung infiltration Hypoxia		
Hepatobiliary disorders		Blood alkaline phosphatase increased	Aspartate aminotransferase increased		
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*		Rheumatoid arthritis aggravated		
Renal and urinary disorders			Glomerulonephritis		

[a] see section 4.8, Description of selected adverse reactions

* includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

SCN patients

MedDRA system organ class	**Adverse reactions**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Blood and lymphatic system disorders	Splenomegaly Anaemia	Thrombocytopenia Splenic rupture	Sickle cell crisis[a]		

Metabolism and nutrition disorders	Hyperuricaemia Blood glucose decreased Blood lactate dehydrogenase increased				
Nervous system disorders	Headache				
Respiratory, thoracic and mediastinal disorders	Epistaxis				
Gastrointestinal disorders	Diarrhoea				
Hepatobiliary disorders	Hepatomegaly Blood alkaline phosphatase increased				
Skin and subcutaneous tissue disorders	Rash	Cutaneous vasculitis Alopecia			

MedDRA system organ class	**Adverse reactions**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Musculoskeletal and connective tissue disorders	Musculoskeletal pain* Arthralgia	Osteoporosis			
Renal and urinary disorders		Haematuria Glomerulonephritis	Proteinuria		
General disorders and administration site conditions		Injection site reaction			

[a] see section 4.8, Description of selected adverse reactions

* includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

Patients with HIV

MedDRA system organ class	**Adverse reactions**					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders		Splenomegaly	Sickle cell crisis[a]			

Musculoskeletal and connective tissue disorders	Musculoskeletal pain*					
Renal and urinary disorder						Glomerulonephritis

[a] see section 4.8, Description of selected adverse reactions
*includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

Description of selected adverse reactions

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).

Cases of capillary leak syndrome have been reported in the post marketing setting 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).

Cancer patients

In randomised, placebo-controlled clinical studies, filgrastim did not increase the incidence of undesirable effects associated with cytotoxic chemotherapy. In those clinical trials, undesirable effects reported with equal frequency in cancer patients treated with filgrastim/chemotherapy and placebo/chemotherapy included nausea and vomiting, alopecia, diarrhoea, fatigue, anorexia, mucositis, headache, cough, skin rash, chest pain, generalised weakness, sore throat, constipation and pain.

In the post-marketing setting cutaneous vasculitis has been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown. The frequency is estimated as uncommon from clinical trial data.

Cases of Sweets syndrome (acute febrile dermatosis) have been reported in the post-marketing setting. The frequency is estimated as uncommon from clinical trial data.

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)

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

Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurred on initial or subsequent treatment in clinical studies and in post-marketing experience. Overall, reports were more common after intravenous 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.

In the post-marketing setting, isolated cases of sickle cell crises have been reported in patients with sickle cell disease (see section 4.4). The frequency is estimated as uncommon from clinical trial data.

Pseudogout has been reported in cancer patients treated with filgrastim, and the frequency is estimated as uncommon from clinical trial data.

PBPC mobilisation in normal donors

Common but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture have been reported in patients and healthy donors following filgrastim administration (see section 4.4).

Pulmonary adverse events such as haemoptysis, pulmonary haemorrhage, lung infiltration, dyspnoea, and hypoxia have been reported (see section 4.4).

Exacerbation of arthritic symptoms has been uncommonly reported.

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

In SCN patients

Undesirable effects include splenomegaly, which maybe progressive in a minority of cases and thrombocytopenia (see section 4.4).

Undesirable effects possibly related to filgrastim therapy and typically occurring in <2% of SCN patients were injection site reaction, headache, hepatomegaly, arthralgia, alopecia, osteoporosis, and rash.

During long-term use cutaneous vasculitis has been reported in 2% of SCN patients.

In patients with HIV

Splenomegaly was reported to be related to filgrastim therapy in <3% of patients. In all cases of splenic enlargement in HIV patients, this was mild or moderate on physical examination and the clinical course was benign; no patients had a diagnosis of hypersplenism and no patients underwent splenectomy. As splenic enlargement is a common finding in patients with HIV infection and is present to varying degrees in most patients with AIDS, the relationship to filgrastim treatment is unclear (see section 4.4).

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.

Other special populations

Elderly patients

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 are insufficient data to evaluate Accofil use in elderly 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. The frequency is estimated as 'common' from clinical trial data.

4.9 Overdose

The effects of Accofil overdose have not been established.

Doses up to 138 μg/kg/day were administered to patients in BMT studies without toxic effects.

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

Accofil is a biosimilar medicinal product.

Mechanism of action
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 by the human body 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.

Treatment with filgrastim in patients undergoing cytotoxic chemotherapy or myeloablative therapy followed by bone marrow transplantation leads to a significant reduction in the incidence, severity and duration of neutropenia and febrile neutropenia, and consequently, fewer admissions to the hospital, shorter duration of hospitalisation and less antibiotics as compared to patients on cytotoxic chemotherapy alone.

Treatment with filgrastim significantly reduces the duration of febrile neutropenia, antibiotic use and hospitalisation after induction chemotherapy for acute myelogenous leukaemia. The incidence of fever and documented infections was not reduced in this setting.

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

Recipients of allogeneic PBPC 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.

Use of filgrastim in patients, children or adults, with severe chronic neutropenia (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

After subcutaneous administration, filgrastim is rapidly absorbed, and peak serum concentrations are attained 2 to 8 hours after dosing. Elimination half-life after intravenous and subcutaneous dosing is usually between 2 and 4 hours. Clearance and half-life are dependent on dose and neutrophil count. When neutrophil mediated clearance is saturated by high filgrastim concentrations or is diminished by neutropenia, the linear clearance pathway predominates and the pharmacokinetics appear linear. The absolute bioavailability of filgrastim after subcutaneous administration is estimated to be 62% for a 375 micrograms dose and 72% for a 750 micrograms dose. After discontinuation of dosing, filgrastim concentrations decrease to endogenous concentrations within 24 hours.

A decrease in filgrastim serum concentrations is evidenced upon multiple dosing in healthy subjects and in cancer subjects before chemotherapy. This increase in clearance of filgrastim is dose dependent, and the magnitude of increase appears closely related to the degree of neutrophilia in the recipients, which is consistent with increased neutrophil-mediated clearance by the expanded neutrophil pool. In subjects receiving filgrastim after chemotherapy, plateau serum concentrations are maintained until onset of haematopoietic recovery.

Distribution

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously. Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/ml for 8 to 16 hours. The volume of distribution in blood is approximately 150 ml/kg.

Elimination

Continuous infusion with filgrastim 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.

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous administration. The mean serum elimination half-life of filgrastim is approximately 3.5 hours, with a clearance rate of approximately 0.6 ml/min/kg.

Pharmacokinetics in Special Populations

Paediatrics

The pharmacokinetics of filgrastim in paediatric patients after chemotherapy is similar to those in adults receiving the same weight-normalised doses, suggesting no age-related differences in the pharmacokinetics of filgrastim.

Geriatrics

Pharmacokinetic data in geriatric patients (> 65 years) are not available.

Renal or hepatic 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. A trend towards higher systemic exposure to filgrastim is observed in patients with ESRD compared with healthy subjects and subjects with creatinine clearance of 30-60 ml/min.

5.3 Preclinical safety data

Carcinogenicity
The carcinogenic potential of filgrastim has not been studied. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolising enzyme system.

Certain malignant cells have been shown to express granulocyte-colony stimulating factor (G-CSF) receptors. The possibility that filgrastim can act as growth factor for any tumor type cannot be excluded.

Impairment of Fertility
Filgrastim had no observed effect on the fertility of male or female rats, or gestation, at doses up to 500 micrograms/kg.

Teratogenicity
There is no evidence from studies in rats and rabbits that filgrastim is teratogenic. An increased incidence of embryo-loss has been observed in rabbits, but no malformation has been seen.

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 saline solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

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

6.3 Interchangeability

Accofil has been developed as a biosimilar product to a reference product named Neupogen. Biosimilar product is similar but not identical to the reference product. It is recommended to consult with healthcare practitioner on the risk of substitution of reference product with biosimilar product.

6.4 Shelf life

36 months.

Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2 °C to 8 °C. From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 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 24 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.

For storage conditions of the diluted medicinal product, see section 6.4.

6.6 Nature and contents of container

Pre-filled syringe with injection needle, with or without a needle safety guard. Package containing one, three, five, seven or ten pre-filled syringe (s), with or without blister and alcohol swabs.

The packs without blister are without needle safety guard. The blister packs are for individual syringes with prefixed needle safety guard. The pre-filled syringes are made from Type I glass with a permanently attached stainless steel needle in the tip and have 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.

Not all pack sizes may be marketed.

6.7 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, Accofil is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

<u>Using the pre-filled syringe with a needle safety guard</u>

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

Disposal

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

7. NAME AND ADDRESS OF PRODUCT REGISTRANT

Accord Healthcare Private Limited
6 Shenton Way, OUE Downtown #38-01
Singapore, 068809

8. NAME AND ADDRESS OF MANUFACTURER

Manufactured by:
Intas Pharmaceuticals Ltd.
Plot No. 423 / P / A, Sarkhej Bavla Highway
Village – Moraiya, Tal – Sanand
Dist. Ahmedabad – 382213
Gujarat State, INDIA