1. NAME OF THE MEDICINAL PRODUCT

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

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each ml of solution contains 96 million units (MU) (equivalent to 960 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.

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.

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. CLINCAL 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 x 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.

Established cytotoxic chemotherapy

Posology

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/m2/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.

Method of administration

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 patients treated with myeloablative therapy followed by bone marrow transplantation

Posology

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.

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 (5µg) /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

Method of administration

Accofil may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Accofil should be diluted in 20 ml of 5% glucose solution (see section 6.6).

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

Posology

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

Method of administration

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.

<u>For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation</u>

Posology

For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU (10 µg)/kg/day 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.

Method of administration

Filgrastim should be given by subcutaneous injection.

In patients with severe chronic neutropenia (SCN)

Posology

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 1-2 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 studies, 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.

Method of administration

For congenital, idiopathic or cyclic neutropenia, filgrastim should be given by subcutaneous injection.

In patients with HIV infection

Posology

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 > 2.0×10^9/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 > 2.0×10^9/L. In clinical studies, dosing with 30 MU (300 µg)/day on 1 - 7 days per week was required to maintain the ANC > 2.0×10^9/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC > 2.0×10^9/L.

Method of administration

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

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 posology 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 patients in the SCN and cancer settings

Sixty-five percent of patients studied in a SCN trial program 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. 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.

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

Accofil is a biosimilar medicinal product of Neupogen. Accofil is not interchangeable or automatically substitutable with Neupogen.

Traceability

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

Information provided below is based on the innovator data (Neupogen, Amgen Europe B.V.).

Special warnings and precautions across indications

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

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.

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.

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*.

Myelodysplastic syndrome or Chronic myeloid leukemia

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.

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
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.

Pulmonary adverse effects
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
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
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

Splenomegaly and splenic rupture
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. 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.

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 MIU/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).

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.

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 $\geq 2.0 \times 10^6$ $CD34^+$ 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

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.

Special precautions in patients with HIV infection

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 trait and sickle cell disease

Sickle cells crises, in some cases fatal, have been reported with the use of filgrastim in subjects with sickle cell trait or sickle cell disease. Physicians should exercise caution when considering the use of filgrastim in patients with sickle cell trait or 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Information provided below is based on the innovator data (Neupogen, Amgen Europe B.V.).

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

Information provided below is based on the innovator data (Neupogen, Amgen Europe B.V.).

Pregnancy

There are no or limited 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 or its metabolites are excreted in human milk. A risk to the breast-feeding child 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

Information provided below is based on the innovator data (Neupogen, Amgen Europe B.V.).

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

Information provided below is based on studies conducted with Accofil.

During clinical studies, 187 healthy subjects were exposed to different doses of Accofil during four phase I studies (KWI-300-101, KWI-300-102, KWI-300-103 and GCSF-SUIN-05SB01-3FA) and 120 breast cancer patients were exposed to 5 mcg/kg/day dose of Accofil during single arm, multicenter phase III study (KWI-300-104). The most commonly reported treatment-related adverse events (TEAEs, in ≥5% subjects) during Phase I PK and PD studies in healthy volunteers are provided in Table 1.

Table 1: Most Commonly Reported Treatment Emergent Adverse Events (in ≥ 5% in Any Group) During Phase I Studies in Healthy Volunteers

Preferred term	**Number of subjects (%)**	
Study KWI-300-101	**Accofil 5 mcg/kg (N = 35)**	**Neupogen 5 mcg/kg (N = 35)**
Back pain	5 (14.3)	5 (13.9)
Rhinitis	4 (11.4)	1 (2.8)
Headache	3 (8.6)	8 (22.2)
Fatigue	2 (5.7)	1 (2.8)
KWI-300-102	**Accofil 75 mcg (N= 37)**	**Neupogen 75 mcg (N= 36)**
Headache	7 (18.9)	11 (30.6)
Nasopharyngitis	4 (10.8)	2 (5.6)
Diarrhea	3 (8.1)	-
Back pain	3 (8.1)	4 (11.1)
Injection site hematoma	3 (8.1)	2 (5.6)
Abdominal pain	2 (5.4)	-

Fatigue	2 (5.4)	2 (5.6)
Feeling hot	1 (2.7)	2 (5.6)
Dysmenorrhea	-	2 (5.6)
KWI-300-102	**Accofil 150 mcg (N = 36)**	**Neupogen 150 mcg (N = 36)**
Headache	6 (16.7)	4 (11.1)
Back pain	1 (2.8)	3 (8.3)
Dizziness	-	3 (8.3)
KWI-300-103	**Accofil 5 mcg/kg/day (N = 36)**	**Neupogen 5 mcg/kg/day (N = 36)**
Back pain	24 (66.7)	21 (58.3)
Headache	14 (38.9)	16 (44.4)
Pharyngolaryngeal pain	3 (8.3)	1 (2.8)
Rhinitis	2 (5.6)	-
Neck pain	2 (5.6)	-
Myalgia	2 (5.6)	1 (2.8)
Fatigue	1 (2.8)	3 (8.3)
Arthralgia	1 (2.8)	3 (8.3)
Nasopharyngitis	1 (2.8)	2 (5.6)
Pain in extremities	-	2 (5.6)
GCSF-SUIN-05SB01-3FA	**Accofil 300 mcg (N = 43)**	**Neupogen 300 mcg (N = 45)**
Neutrophil count decreased	37 (86)	Neupogen-EU, 34 (75.6) Neupogen-US, 34 (75.6)
Eosinophil count increased	7 (16.3)	Neupogen-EU, 7 (15.6) Neupogen-US, 5 (11.1)
Blood pressure decreased	6 (14)	Neupogen-EU, 6 (13.3) Neupogen-US, 5 (11.1)
Headache	5 (11.6)	Neupogen-EU, 5 (11.1) Neupogen-US, 6 (13.3)
Neutrophil count increased	4 (9.3)	Neupogen-EU, 5 (11.1) Neupogen-US, 3 (6.7)

In the single arm study in breast cancer patients (KWI-300-104) treated with 5 mcg/kg/day Accofil, the majority of patients (110/120; 91.7%) reported at least one AE during the duration of the trial. The most common (reported in ≥5% of patients) AEs are summarized in Table 2.

Table 2: Treatment Emergent Adverse Events (TEAEs) Reported for ≥ 5% of Breast Cancer Patients (Study KWI-300-104)

System organ class **Preferred term**	**Accofil 5 mcg/kg/day (N=120)**
	Number (%) of patients
Total number of AEs Number (%) of patients with at least 1 AE	1216 110 (91.67)
Ear and labyrinth disorders	

Vertigo	11 (9.17)
Gastrointestinal disorders	
Nausea	64 (53.33)
Diarrhea	22 (18.33)
Vomiting	12 (10.00)
Abdominal pain upper	7 (5.83)
Dyspepsia	7 (5.83)
Abdominal pain	6 (5.00)
General disorders and administration site conditions	
Fatigue	24 (20.00)
Pyrexia	7 (5.83)
Asthenia	6 (5.00)
Metabolism and nutrition disorders	
Anorexia	6 (5.00)
Musculoskeletal and connective tissue disorders	
Bone pain	80 (66.67)
Nervous system disorders	
Headache	29 (24.17)
Dizziness	16 (13.33)
Respiratory, thoracic and mediastinal disorders	
Pharyngolaryngeal pain	9 (7.50)
Skin and subcutaneous tissue disorders	
Alopecia	36 (30.00)

Note: The total number of treatment emergent adverse events count included all patient events. At each level of summarization, a patient was counted once if he or she reported 1 or more events. Only the most severe event was counted.
Medical Dictionary for Regulatory Activities Version 10.0 was used.

Immunogenicity:

In single-arm safety study in breast cancer patients (KWI-300-104), immunogenicity assessment was performed on samples prior to initiation of each chemotherapy cycle and thereafter in the safety follow-up phase in weeks 20, 24, 36 and 48 relative to the first chemotherapy treatment. There were no signs of immunogenicity either detected by clinical observation or by the laboratory. None of the samples were confirmed as positive in the Confirmatory assay. In addition, there were no clinical manifestations of antibody formation, such as hypersensitivity reactions or decrease in ANC observed after completion of the treatment period.

Information provided below is based on the innovator data (Neupogen, Amgen Europe B.V.).

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.

Tabulated list 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.

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.

MedDRA system organ class	**Adverse reactions**					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
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	-	-
Immune system disorders			Graft versus Host Disease[b] Drug hypersensitivity[a] Hypersensitivity	Anaphylactic reaction	-	-
Metabolism and nutrition disorders		Decreased Appetite[e] Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout A (Chondrocalcinosis Pyrophosp hate) 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] 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 abnormalit y Glomerulo nephritis	-	-
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 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] Adverse events with higher incidence in Filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy

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 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).

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.

Sweets syndrome
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.

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 uncommonly 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 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.

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

Leukocytosis
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.

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

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 are 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.

4.9 Overdose

The effects of Accofil overdose 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.

Pharmacodynamic effects

Information provided below is based on studies conducted with Accofil.

Accofil has been compared to the reference product, Neupogen, in healthy volunteers in four phase 1 studies.

KWI-300-101 was a single-dose, randomized, double-blind, two-way, crossover, comparative study in healthy volunteers to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Accofil and Neupogen. Subjects were randomized to receive single intravenous (IV) dose of 5 microgram (mcg)/kg of either Accofil or Neupogen. The PD results from the per protocol (PP) population are summarized in Table 3. Overall, PD profile of Accofil and Neupogen was found to be similar after a single IV dose of 5 mcg/kg.

Table 3: Pharmacodynamic Parameters of Per Protocol Population Following a Single Intravenous Infusion of 5 mcg/kg Accofil or Neupogen to Healthy Volunteers (Study KWI-300-101)

Endpoint	Accofil (N=35)	Neupogen (N=35)	GM ratio (Accofil/Neupogen)	90% CI (%)
ANC C_{max} (cells × 10^9/L)	19.02 (4.35)	19.28 (5.21)	99.5%	93.6 – 105.8
ANC AUC_{0-72h} (min*G/L)	46137.4 (8608)	46601.5 (9321.6)	-	-

Values presented as mean (SD).
ANC: Absolute neutrophil count; ANC C_{max}: Maximum observed ANC over the sampling interval; AUC_{0-72}: Area under the curve from 0 hours measured up to 72 hours; CI: Confidence interval; GM: geometric mean

KWI-300-102 was a single-dose, randomized, double-blind, two-way, crossover, comparative study in healthy volunteers to evaluate the PK and PD of Accofil and Neupogen. Subjects were randomized to receive single subcutaneous (SC) dose of 75 mcg and 150 mcg of Accofil or

Neupogen. The PD results from the PP population are summarized in Table 4. Overall, PD profile of Accofil and Neupogen was found to be similar after a single SC dose of 75 mcg and 150 mcg.

Table 4: Pharmacodynamic Parameters of Per Protocol Population Following a Single Subcutaneous Injection of 75 and 150 mcg Accofil or Neupogen to Healthy Volunteers (Study KWI-300-102)

Endpoint	Accofil	Neupogen	GM ratio (Accofil/Neupogen)	95% CI (%)
75 mcg				
	N=33	N=33		
ANC C_{max} (G/L)	17.13 (3.74)	18.60 (4.11)	92.0%	87.9 – 96.2
ANC AUC_{0-72h} (min*G/L)	35076.8 (6526.3)	37009.8 (7622.5)	-	-
150 mcg				
	N=35	N=35		
ANC C_{max} (G/L)	19.04 (3.83)	19.59 (3.29)	96.3%	91.9 – 101.0
ANC AUC_{0-72h} (min*G/L)	43209.3 (7921.5)	43979.6 (6866.4)	-	-

Values presented as mean (SD).
ANC: Absolute neutrophil count; C_{max}: Maximum observed ANC over the sampling interval; AUC_{0-72}: Area under the curve from 0 hours to 72 hours; CI: Confidence interval; GM: geometric mean

KWI-300-103 was a repeat dose, randomized, double-blind, active and placebo-controlled, parallel group, comparative study to evaluate the PK and PD of Accofil and Neupogen in healthy volunteers. Subjects were randomized to receive daily SC dose of Accofil or Neupogen 5 mcg/kg/day for 4 days, or placebo for 4 days. The PD results from the PP population are summarized in Table 5. Overall, PD profile of Accofil and Neupogen was found to be similar after repeated SC dosing 5 mcg/kg/day.

Table 5: Pharmacodynamic Parameters of Per Protocol Population Following Four Daily Subcutaneous Injections of 5 mcg/kg Accofil or Neupogen to Healthy Volunteers (Study KWI-300-103)

Endpoint	Accofil (N=35)	Neupogen (N=34)	GM ratio (Accofil/Neupogen)	90% CI (%)
ANC C_{max} (G/L) Day 4	30.54 (6.15)	32.27 (7.68)	95.2%	87.29 – 103.85
ANC $C_{max-24h}$ (G/L) Day 1	21.04 (3.68)	21.96 (4.62)	-	-
ANC AUC_{0-24h} (min*G/L)	22974.9 (3878.1)	23873.8 (4679.4)	-	-

Values presented as mean (SD).
ANC: Absolute neutrophil count; C_{max}: Maximum observed ANC over the sampling interval; AUC_{0-96h}: area under the curve from 0 hours up to 96 hours; CI: Confidence interval; GM: geometric mean

In KWI-300-103, absolute CD34+ cell count was also assessed on study days 1 (i.e., baseline) and

5 (after 4 treatment doses). The mean±SD CD34+ cell counts were 2 ± 0.80/µL for Accofil and 1.86 ± 0.75/µL for Neupogen at baseline. Accofil increased CD34+ cell counts to 27.65 ± 16.54/µL and Neupogen increased CD34+ counts to 24.48 ± 14.98 /µL on day 5.

GCSF-SUIN-05SB01-3FA was a double-blind, single-dose, randomized, three-way, crossover, comparative study in healthy volunteers to evaluate the PK and PD of Accofil, Neupogen-US and Neupogen-EU. Subjects were randomized to receive a single SC dose of 300 mcg Accofil, Neupogen-US or Neupogen-EU. The PD results from the study are summarized in Table 6. Overall, PD profile of Accofil was found to be similar to Neupogen-US and Neupogen-EU after a single SC dose of 300 mcg.

Table 6: Pharmacodynamic Parameters Following a Single Subcutaneous Injection of 300 mcg Accofil, Neupogen-EU or Neupogen-US to Healthy Volunteers (Study GCSF-SUIN-05SB01-3FA)

Endpoint	Accofil (N=43)	Neupogen-US (N=43)	Neupogen-EU (N=44)	GM ratio (Accofil/Neupogen)	90% CI (%)
ANC C_{max} (cells × 10^9/L)	20.68	20.49	19.92	1.00 (vs. Neupogen-US); 1.03 (vs. Neupogen-EU)	0.96-1.05 (vs. Neupogen-US); 0.99-1.08 (vs. Neupogen-EU)
ANC AUC_{0-t} (hr*cells × 10^9/L)	982.31	964.93	952.13	1.00 (vs. Neupogen-US); 1.03 (vs. Neupogen-EU)	0.97-1.04 (vs. Neupogen-US); 1.00-1.06 (vs. Neupogen-EU)

Values presented as mean.
ANC: Absolute neutrophil count; C_{max}: Maximum observed ANC over the sampling interval; AUC_{0-t}: area under the curve from 0 hours up to sampling time; CI: Confidence interval; GM: geometric mean

Clinical efficacy:

Efficacy of Accofil was evaluated as part of non-comparative, multicenter, repeat-dose study in breast cancer patients receiving TAC (docetaxel, doxorubicin and cyclophosphamide) chemotherapy regimen (KWI-300-104). One-hundred and twenty patients were administered with 5 mcg/kg/day SC dose of Accofil on the second day of chemotherapy cycle and was continued up to 14 days or until post-nadir ANC recovery to normal or near-normal values by laboratory standards, whoever occurs first. Patients were treated for total 6 cycles. The main efficacy endpoint was duration of severe neutropenia (occurrence of ANC < 0.5 x 10^9/L) in cycle 1.

The mean (SD) duration of severe neutropenia in cycle was 1.40 (1.07) days. Incidence of severe neutropenia and febrile neutropenia was 77.5% and 2.5%, respectively in cycle 1. No incidence of febrile neutropenia was reported in other cycles. Incidence of severe neutropenia was 3.51%, 7.02%, 4.38%, 7.96% and 10.62%, in cycles 2, 3, 4, 5 and 6 respectively. Frequency of grade 3 and 4 neutropenia in cycle 1 was 88.33% and 77.5% respectively and it was lower in subsequent cycles.

Information provided below is based on the innovator data (Neupogen, Amgen Europe B.V.).

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 *severe chronic neutropenia* (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 peripheral blood. These autologous peripheral blood progenitor cells (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 graft versus host disease (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 micrograms/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 adults with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in absolute neutrophil count (ANCs) 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 treatments. 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

Information provided below is based on studies conducted with Accofil.

Accofil has been compared to the reference product in healthy volunteers in four phase 1 studies. KWI-300-101 was a single-dose, randomized, double-blind, two-way, crossover, comparative study in healthy volunteers to evaluate the PK and PD of Accofil and Neupogen. Subjects were randomized to receive single IV dose of 5 mcg/kg Accofil or Neupogen. The PK results are summarized in Table 7. Overall, PK profile of Accofil and Neupogen was found to be similar.

Table 7: Pharmacokinetic Parameters of Per Protocol Population Following a Single Intravenous Infusion of 5 mcg/kg Accofil or Neupogen to Healthy Volunteers (Study KWI-300-101)

Endpoint	Accofil (N=35)	Neupogen (N=35)	GM ratio (Accofil/Neupogen)	90% CI (%)
AUC_{0-32} (min*pg/mL)	22047494 (4060115)	24340789 (4530366)	90.6%	88.7 - 92.7
C_{max} (pg/mL)	103272.4 (15031.9)	111567 (15688.3)	92.5%	90.3 - 94.7
AUC_{0-inf} (min*pg/ml)	22075297 (4065640)	24366534 (4535283)	90.7%	88.7 – 92.7
T_{max} (min)	16.3 (9.1)	16.0 (5.5)	-	-

Values presented as mean (SD).
AUC_{0-32h}: Area under the concentration-time curve from 0 hours up to 32 hours; C_{max}: Maximum plasma concentration; T_{max}: Time at which C_{max} is achieved; SD: Standard Deviation; GM: geometric mean

KWI-300-102 was a single-dose, randomized, double-blind, two-way, crossover, comparative study in healthy volunteers to evaluate the PK and PD of Accofil and Neupogen. Subjects were randomized to receive single SC dose of 75 mcg and 150 mcg of Accofil or Neupogen. The PK of Accofil and Neupogen was evaluated in subjects receiving 150 mcg dose. The PK results from the PP population are summarized in Table 8. Overall, PK profile of Accofil and Neupogen was found to be similar after a single SC dose of 150 mcg.

Table 8: Pharmacokinetic Parameters of Per Protocol Population Following a Single Subcutaneous Injection of 150 mcg Accofil or Neupogen to Healthy Volunteers (Study KWI-300-102)

Endpoint	Accofil 150 µg (N=35)	Neupogen 150 µg (N=35)	GM ratio (Accofil/Neupogen)	90% CI (%)
AUC_{0-72} (min*ng/mL)	3275.7 (919.5)	3414.6 (1093.5)	96.8%	91.0 – 103.0
C_{max} (ng/mL)	7.72 (2.35)	8.35 (3.05)	94.6%	85.9 – 104.1
AUC_{0-inf} (min*ng/ml)	3282.7 (920.7)	3419.7 (1093.7)	96.8%	91.0 – 103.0
T_{max} (min)	278.6 (41.5)	283.7 (54.1)	-	-

Values presented as mean (SD).
AUC_{0-72h}: Area under the concentration-time curve from 0 hours up to 72 hours; C_{max}: Maximum plasma concentration; T_{max}: Time at which C_{max} is achieved; SD: Standard Deviation; GM: geometric mean.

KWI-300-103 was a repeat dose, randomized, double-blind, active and placebo-controlled, parallel group, comparative study in healthy volunteers to evaluate the PK and PD of Accofil and Neupogen. Subjects were randomized to receive daily SC dose of Accofil or Neupogen 5 mcg/kg/day for 4 days, or placebo for 4 days. The PK results from the PP population are summarized in Table 7. Overall, PK profile of Accofil and Neupogen was found to be similar

after repeated SC dosing of 5 mcg/kg/day.

Table 9: Pharmacokinetic Parameters of Per Protocol Population Following a Single and Four Daily Subcutaneous Injections of 5 mcg/kg Accofil or Neupogen to Healthy Volunteers (Study KWI-300-103)

Endpoint	Accofil (N=35)	Neupogen (N=34)	GM ratio (Accofil/Neupogen)	90% CI (%)
AUC_{0-24h} (min*ng/mL) Day 1	11734.8 (2737)	11839.4 (3292.4)	100.2%	90.3 – 111.1
AUC_{ss} (min*ng/mL) Day 4	5440.8 (1484.6)	5387.6 (1790.2)	102.3%	91.1 – 114.9
C_{max} (ng/mL) Day 1	25.92 (6.95)	25.54 (7.81)	102.2%	91.3 – 114.5
AUC_{0-inf} (min*ng/ml) Day 1	11803.8 (2751.5)	11917 (3307.9)	100.1%	90.29 – 110.98
T_{max} (min) Day 1	297.4 (35.2)	307.1 (33.1)	-	-

Values presented as mean (SD).
AUC_{0-24h}: Area under the concentration-time curve from 0 hours up to 24 hours; AUC_{ss}: Area under the plasma concentration-time curve in steady state, following the last filgrastim administration (trial day 4) up to the last measured filgrastim concentration; C_{max}: Maximum plasma concentration; T_{max}: Time at which Cmax is achieved; SD: Standard Deviation; CI: Confidence interval; GM: geometric mean.

GCSF-SUIN-05SB01-3FA was a double-blind, single-dose, randomized, three-way, crossover, comparative study in healthy volunteers to evaluate the PK and PD of Accofil, Neupogen-US and Neupogen-EU. Subjects were randomized to receive a single SC dose of 300 mcg Accofil, Neupogen-US or Neupogen-EU. The PK results from the study are summarized in Table 10. Overall, PK profile of Accofil was found to be similar to Neupogen-US and Neupogen-EU after a single SC dose of 300 mcg.

Table 10: Pharmacokinetic Parameters Following a Single Subcutaneous Injection of 300 mcg Accofil, Neupogen-EU or Neupogen-US to Healthy Volunteers (Study GCSF-SUIN-05SB01-3FA)

Endpoint	Accofil (N=43)	Neupogen-US (N=43)	Neupogen-EU (N=44)	GM ratio (Accofil/Neupogen)	90% CI (%)
AUC_{0-t} (pg*h/ml)	200720.00	192379.97	186404.48	1.08 (vs. Neupogen-US); 1.10 (vs. Neupogen-EU)	1.02-1.14 (vs. Neupogen-US); 1.04-1.16 (vs. Neupogen-EU)
C_{max} (pg/ml)	24212.80	22456.87	21835.92	1.10 (vs. Neupogen-US); 1.11 (vs. Neupogen-EU)	1.01-1.20 (vs. Neupogen-US); 1.02-1.21 (vs. Neupogen-EU)
AUC_{inf} (pg*h/ml)	202126.78	193710.54	187937.67	1.08 (vs. Neupogen-US); 1.09 (vs. Neupogen-EU)	1.02-1.14 (vs. Neupogen-US); 1.04-1.15 (vs. Neupogen-

					EU)
T_{max} (h)	5.00	5.00	5.00	0.97 (vs. Neupogen-US); 0.99 (vs. Neupogen-EU)	0.88-1.06 (vs. Neupogen-US); 0.91-1.07 (vs. Neupogen-EU)

Values presented as mean.
AUC_{0-t}: Area under the concentration-time curve from 0 hours up to sampling time; AUC_{inf}: Area under the concentration-time curve from 0 hours up to infinity; C_{max}: Maximum plasma concentration; Kel: elimination rate constant; T_{max}: Time at which C_{max} is achieved; SD: Standard Deviation; GM: geometric mean

Information provided below is based on the innovator data (Neupogen, Amgen Europe B.V.).

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 or 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 half-lives.

Linearity

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 10ng/ml for 8 to 16 hours. The volume of distribution in blood is approximately 150ml/kg.

5.3 Preclinical safety data

Information provided below is based on studies conducted with Accofil.

Preclinical studies of Accofil included two comparative pharmacodynamic studies, a non-comparative acute as well as a repeat-dose toxicity studies, a comparative repeat-dose toxicity and a non-comparative as well as a comparative local tolerance studies.

The pharmacodynamic effects of Accofil and Neupogen were found to be similar in terms of neutrophil count restoration in cyclophosphamide-induced neutropenia in mice at different dose levels during two studies. Accofil and Neupogen led to dose-dependent increase in total leukocyte count – in particular in neutrophils, during repeat-dose toxicity study in rat.

During non-comparative acute toxicity studies, Accofil was well tolerated at dose levels up to 5000 µg/kg by intravenous and subcutaneous route in rat and mouse. During non-comparative

repeat-dose toxicity studies, Accofil was well tolerated at dose levels up to 250 µg/kg/day for 28 days by intravenous and subcutaneous route in rat and mouse.

In a comparative repeat-dose toxicity study, Wistar rats were given subcutaneous doses of 50, 150 and 500 µg/kg/day Accofil or Neupogen (150 µg/kg/day) for 28 days. All toxic effects observed in the study, are known pharmacological effect of recombinant G-CSF and have previously been described in published literature. Animals treated with Accofil and Neupogen showed an increase in alkaline phosphatase levels and spleen weight, with both these effects being dose dependent. The change in spleen weight was accompanied by histiocytosis frequently combined with an increased hemopoiesis, observed in both, in Accofil and Neupogen treated animals. A thickening of spleen capsule due to a fibrosis was also observed in Accofil and Neupogen treated animals. Swelling of the hindlimbs or the joints of the hindlegs were observed in all dose groups when compared to the control group. A dose-dependent increase in white blood cells, in particular in neutrophils, was found with both, Accofil and Neupogen. This effect was apparent on study Day 14 and at the end of the treatment period. The single and repeated daily administration of Accofil and Neupogen at three different doses (50, 150 and 500 µg/kg) by intravenous and subcutaneous route resulted in a dose-linear exposure of filgrastim.

In local tolerance studies in rabbits, a single intramuscular and paravenous administration of Accofil was well tolerated.

Information provided below is based on the innovator data (Neupogen, Amgen Europe B.V.).

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 leukocytes, 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 fetal weight were observed.

Based on reported data for another filgrastim product, comparable findings plus increased fetal 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-fetal 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 fetal 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 medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

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.

6.4 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 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 6.3.

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 or five 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, 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 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.

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