NEXFIL
(Filgrastim)

300mcg

Pre-filled syringe

COMPOSITION

Each pre-filled syringe (0.5mL) contains:
Filgrastim 300mcg
(Product Complies to Ph. Eur. Specifications)

THERAPEUTIC INDICATIONS

Filgrastim 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 leukemia 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 Filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

Filgrastim is indicated for the mobilization of peripheral blood progenitor cells (PBPCs).

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an ANC of ≤ 0.5 x 10^9/l, and a history of severe or recurrent infections, long term administration of Filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Filgrastim 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.

DOSAGE AND METHOD OF ADMINISTRATION

Filgrastim therapy should only be given in collaboration with an oncology centre which has experience in G-CSF treatment and hematology and has the necessary diagnostic facilities. The mobilization and apheresis procedures should be performed in collaboration with an oncology-hematology centre with acceptable experience in this field and where the monitoring of hematopoietic progenitor cells can be correctly performed.

Established cytotoxic chemotherapy

Dosage

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

Daily dosing with Filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumors, lymphomas, and lymphoid leukemia, 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 leukemia 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 to 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 given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minutes. 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

Dosage

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

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

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

Method of administration

Filgrastim may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 ml of 5% glucose solution

For the mobilization of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

Dosage

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

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

Method of administration

Filgrastim for PBPC mobilization when used alone:

Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions Filgrastim should be diluted in 20 ml of 5% glucose solution

Filgrastim for PBPC mobilization after myelosuppressive chemotherapy:

Filgrastim should be given by subcutaneous injection.

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

Dosage

For PBPC mobilization in normal donors, Filgrastim should be administered at 1.0 MU (10 µg)/kg/day for 4 to 5 consecutive days. Leukapheresis should

be started at day 5 and continued until day 6 if needed in order to collect 4 x 10^6 $CD34^+$ cells/kg recipient bodyweight.

Method of administration

Filgrastim should be given by subcutaneous injection.

In patients with severe chronic neutropenia (SCN)

Dosage

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

Method of administration

Congenital, idiopathic or cyclic neutropenia: Filgrastim should be given by subcutaneous injection.

In patients with HIV infection

Dosage

For reversal of neutropenia:

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

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

For 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 µg)/dayis recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2.0 x 10^9/l. In clinical studies, dosing with 30 MU (300 µg)/day on 1 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.

Method of administration

Reversal of neutropenia or maintaining normal neutrophil counts: Filgrastim should be given by subcutaneous injection.

Older people

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

Patients with renal impairment

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

Paediatric use in the SCN and cancer settings

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

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

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

Important Administration Instructions

Filgrastim is supplied in single-dose prefilled syringes (for subcutaneous use). Prior to use, remove the prefilled syringe from the refrigerator and allow Filgrastim to reach room temperature for a minimum of 30 minutes and a maximum of 24 hours. Discard any vial or prefilled syringe left at room temperature for greater than 24 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit (the solution is clear and colorless). Do not administer Filgrastim if particulates or discoloration are observed.

Discard unused portion of Filgrastim in prefilled syringes. Do not save unused drug for later administration.

Subcutaneous Injection

Inject Filgrastim subcutaneously in the outer area of upper arms, abdomen, thighs, or upper outer areas of the buttock. If patients or caregivers are to administer Filgrastim, instruct them in appropriate injection technique and ask them to follow the subcutaneous injection procedures

Training by the healthcare provider should aim to demonstrate to those patients and caregivers how to measure the dose of Filgrastim, and the focus should be on ensuring that a patient or caregiver can successfully perform all the steps. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the product successfully, you should consider whether the patient is an appropriate candidate for self-administration of Filgrastim or whether the patient would benefit from a different Filgrastim presentation. If a patient or caregiver experiences difficulty measuring the required dose, especially if it is other than the entire contents of the Filgrastim prefilled syringe, use of the Filgrastim vial may be considered.

If the patient or caregiver misses a dose of Filgrastim, instruct them to contact their healthcare provider.

Administration Instructions for the Prefilled Syringe

Persons with latex allergies should not administer the Filgrastim prefilled syringe, because the needle cap contains dry natural rubber (derived from latex).

Special precautions for storage

Store at 2 to 8°C.

For storage conditions after dilution of the medicinal product- Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Accidental exposure to freezing temperatures does not adversely affect the stability of Filgrastim.

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

Special precautions for disposal and other handling

If required, Filgrastim may be diluted in 5% glucose.

Dilution to a final concentration less than 0.2 MU (2 µg) per ml is not recommended at any time.

The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

For patients treated with filgrastim diluted to concentrations below 1.5 MU (15 µg) per ml, human serum albumin (HSA) should be added to a final concentration of 2 mg/ml.

Example: In a final injection volume of 20 ml, total doses of filgrastim less than 30 MU (300 µg) should be given with 0.2 ml of 20% human albumin solution Ph. Eur. added.

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

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

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

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients

WARNINGS AND PRECAUTIONS

Special warning and precautions across indications

Hypersensitivity

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

Pulmonary adverse effects

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

Glomerulonephritis

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

Capillary leak syndrome

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after granulocyte colony-stimulating factor administration, and is characterised by hypotension, hypoalbuminemia, 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.

Splenomegaly and Splenic rupture

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

Malignant cell growth

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

Myelodysplastic syndrome or Chronic myeloid leukaemia

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

Acute myeloid leukaemia

In view of limited safety and efficacy data in patients with secondary AML, Filgrastim should be administered with caution. The safety and efficacy of Filgrastim administration in *de novo* AML patients aged < 55 years with good cytogenetics have not been established.

Thrombocytopenia

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

Leukocytosis

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

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Rate 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 warning and precautions associated with co-morbidities

Special precautions in sickle cell trait and sickle cell disease

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

Osteoporosis

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

Special precautions in cancer patients

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

Risks associated with increased doses of chemotherapy

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

Effect of chemotherapy on erythrocytes and thrombocytes

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

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

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 GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation.

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

Special precautions in patients undergoing PBPC mobilisation

Mobilisation

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

Prior exposure to cytotoxic agents

Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield (≥ 2.0 x 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 BCNU together with Filgrastim, has been shown to be effective for progenitor mobilisation. When PBPC transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment, not requiring progenitor support should be considered.

Assessment of progenitor cell yields

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

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

The recommendation of a minimum 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 appear to correlate with more rapid recovery, those below with slower recovery.

Special precautions in normal donors undergoing PBPC mobilisation

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

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

The safety and efficacy of Filgrastim have not been assessed in normal donors < 16 years or > 60 years.

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

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

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis.

Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal.

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.

Special precautions in recipients of allogeneic PBPCs mobilised with Filgrastim

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

Special precautions in SCN patients

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

Blood cell counts

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

Transformation to leukaemia or myelodysplastic syndrome

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

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical trial patients with SCN treated

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

Other special precautions

Causes of transient neutropenia, such as viral infections should be excluded.

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

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

Special precautions in patients with HIV infection

Blood cell counts

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

Risk associated with increased doses of myelosuppressive medications

Treatment with Filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medications. As a result of the potential to receive higher doses or a greater number of these medications with Filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended.

Infections and malignancies causing myelosuppression

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

All patients

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

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

DRUG INTERACTIONS

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

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

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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

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

Filgrastim is not recommended during pregnancy.

Breast-feeding

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

Fertility

Filgrastim did not affect reproductive performance or fertility in male or female rats.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Filgrastim may have a minor influence on the ability to drive and use machines. Dizziness may occur following the administration of Filgrastim.

ADVERSE DRUG REACTIONS

a. Summary of the safety profile

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

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

b. Tabulated summary of adverse reactions

The data in the 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.

MedDRA system organ class	**Adverse reactions**				
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1000)**	**Very rare (< 1/10,000)**

Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection			
Blood and lymphatic system disorders	Thrombocytopenia Anaemia[e]	Splenomegaly[a] Haemoglobin decreased[e]	Leukocytosis[a]	Splenic rupture[a] Sickle cell anaemia with crisis	
Immune system disorders			Hypersensitivity Drug hypersensitivity[a] Graft versus Host Disease[b]	Anaphylactic reaction	
Metabolism and nutrition disorders		Decreased Appetite[e] Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout[a] (Chondrocalcinosis Pyrophosphate) Fluid volume disturbances	
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache[a]	Dizziness Hypoaesthesia Paraesthesia			
Vascular Disorders		Hypertension Hypotension	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] Pulmonary haemorrhage Interstitial lung disease[a] Lung infiltration[a] Hypoxia		
Gastrointestinal disorders	Diarrhoea[a, e] Vomiting[a, e] Nausea[a]	Oral Pain Constipation[e]			
Hepatobiliary disorders		Hepatomegaly Blood alkaline phosphatase increased	Aspartate aminotransferase increased Gamma-glutamyl transferase increased		
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Rash maculo-papular	Cutaneous vasculitis[a] Sweets syndrome (acute febrile neutrophilic dermatosis)	
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	Glomerulonephritis Urine abnormality	
General disorders and administration site conditions	Fatigue[a] Mucosal inflammation[a] Pyrexia	Chest pain[a] Pain[a] Asthenia[a] Malaise[e] Oedema peripheral[e]	Injection site reaction		
Injury, poisoning and procedural complications		Transfusion reaction[e]			

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

[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section c)

[c] Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

[d] Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC 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

c. Description of selected adverse reactions

Hypersensitivity

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

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.

Splenomegaly and Splenic rupture

Cases of splenomegaly and splenic rupture have been reported following administration of filgrastim. Some cases of splenic rupture were fatal.

Capillary leak syndrome

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

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.

Leukocytosis

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

Sweets syndrome

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

Pseudogout (chondrocalcinosis pyrophosphate)

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

GvHD

There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation.

d. Paediatric population

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

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

e. Other special populations

Geriatric Use

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

OVERDOSE

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Cytokines, ATC Code: L03AA02

Mechanism of Action

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation.

Endogenous G-CSF is a lineage-specific colony-stimulating factor that is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens). G-CSF is not species-specific and has been shown to have minimal direct *in vivo* or *in vitro* effects on the production or activity of hematopoietic cell types other than the neutrophil lineage.

Pharmacodynamics

In phase 1 studies involving 96 patients with various nonmyeloid malignancies, FILGRASTIM administration resulted in a dose-dependent increase in circulating neutrophil counts over the dose range of 1 to 70 mcg/kg/day. This increase in neutrophil counts was observed whether FILGRASTIM was administered intravenous (1 to 70 mcg/kg twice daily), subcutaneous (1 to 3 mcg/kg once daily), or by continuous subcutaneous infusion (3 to 11 mcg/kg/day). With discontinuation of FILGRASTIM therapy, neutrophil counts returned to baseline in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic (measured by migration under agarose using N-formyl-methionyl-leucyl-phenylalanine [fMLP] as the chemotaxin) activity *in vitro*.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving FILGRASTIM; however, the percentage of monocytes in the differential count remained within the normal range. Absolute counts of both eosinophils and basophils did not change and were within the normal range following administration of FILGRASTIM. Increases in lymphocyte counts following FILGRASTIM administration have been reported in some normal subjects and patients with cancer.

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards earlier granulocyte progenitor cells (left shift) , including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. In addition, , Dohle bodies, increased granulocyte granulation, and hypersegmented neutrophils have been observed. Such changes were transient and were not associated with clinical sequelae, nor were they necessarily associated with infection.

Pharmacokinetic Properties

Filgrastim exhibits nonlinear pharmacokinetics. Clearance is dependent on filgrastim concentration and neutrophil count: G-CSF receptor-mediated clearance is saturated by high concentration of FILGRASTIM and is diminished by neutropenia. In addition, filgrastim is cleared by the kidney.

Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg of filgrastim resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. After intravenous administration, the volume of distribution averaged 150 mL/kg and the elimination half-life was approximately 3.5 hours in both normal subjects and cancer subjects. Clearance rates of filgrastim were approximately 0.5 to 0.7 mL/minute/kg. Single parenteral doses or daily intravenous doses, over a 14-day period, resulted in comparable half-lives. The half-lives were similar for intravenous administration (231 minutes, following doses of 34.5 mcg/kg) and for subcutaneous administration (210 minutes, following FILGRASTIM dosages of 3.45 mcg/kg). Continuous 24-hour intravenous infusions of 20 mcg/kg over an 11 to 20-day period produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated. The absolute bioavailability of filgrastim after subcutaneous administration is 60% to 70%.

Specific Populations

Patients Acutely Exposed to Myelosuppressive Doses of Radiation

The pharmacokinetics of filgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetics data in irradiated non-human primates, the area under the time-concentration curve (AUC), reflecting the exposure to filgrastim in non-human primates at 10 mcg/kg dose of FILGRASTIM, appears to be similar to that in humans at 5 mcg/kg. Simulations conducted using the population pharmacokinetic model indicates that the exposures to filgrastim at a FILGRASTIM dose of 10 mcg/kg in patients acutely exposed to myelosuppressive doses of radiation are expected to exceed the exposures at a dose of 10 mcg/kg in irradiated non-human primates.

Pediatric Patients

The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adult patients receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim

Renal Impairment

In a study with healthy volunteers, subjects with moderate renal impairment, and subjects with end-stage renal disease (n = 4 per group), higher serum concentrations were observed in subjects with end-stage renal disease. However, dose adjustment in patients with renal impairment is not necessary.

Hepatic Impairment

Pharmacokinetics and pharmacodynamics of filgrastim are similar between subjects with hepatic impairment and healthy subjects (n = 12/group). The study included 10 subjects with mild hepatic impairment (Child-Pugh Class A) and 2 subjects with moderate hepatic impairment (Child-Pugh Class B). Therefore, filgrastim dose adjustment for patients with hepatic impairment is not necessary.

Summary of Clinical Studies

Patients with Cancer Receiving Myelosuppressive Chemotherapy

The safety and efficacy of FILGRASTIM to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).

In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21 day cycles. Patients were randomized to receive FILGRASTIM (n = 99) at a dose of 230 mcg/m2 (4 to 8 mcg/kg/day) or placebo (n = 111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease.

The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an ANC < 1,000/mm3 and temperature > 38.2°C. Treatment with FILGRASTIM resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, 40% for FILGRASTIM-treated patients and 76% for placebo-treated patients ($p < 0.001$). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm3); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of FILGRASTIM to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, *de novo* AML (Study 4).

In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous FILGRASTIM (n = 259) at a dose of 5 mcg/kg/day or placebo (n = 262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥ 1,000/mm3 for 3 consecutive days or ≥ 10,000/mm3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white blood cell count (65% < 25,000/mm3 and 27% > 100,000/mm3); 29% unfavorable cytogenetics.

The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm3. Treatment with FILGRASTIM resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, FILGRASTIM-treated patients 14 days, placebo-treated patients 19 days ($p = 0.0001$: difference of 5 days (95% CI: -6.0, -4.0)). There was a reduction in the median duration of intravenous antibiotic use, FILGRASTIM-treated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, FILGRASTIM-treated patients: 20 days versus placebo-treated patients: 25 days.

There were no statistically significant differences between the FILGRASTIM and the placebo groups in complete remission rate (69% - FILGRASTIM, 68% - placebo), median time to progression of all randomized patients (165 days - FILGRASTIM, 186 days - placebo), or median overall survival (380 days - FILGRASTIM, 425 days - placebo).

Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of FILGRASTIM to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of FILGRASTIM to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo-controlled trial (Study 10).

In Study 6, patients with Hodgkin's disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"), and patients with non-Hodgkin's lymphoma received intravenous BCNU,

etoposide, cytosine arabinoside and melphalan ("BEAM"). There were 54 patients randomized 1:1:1 to control, FILGRASTIM 10 mcg/kg/day, and FILGRASTIM 30 mcg/kg/day as a 24-hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin's disease and 31% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm3) occurred in the FILGRASTIM-treated groups versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group [11 days in the combined treatment groups, p = 0.004]).

In Study 9, patients with Hodgkin's disease and non-Hodgkin's lymphoma received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"). There were 43 evaluable patients randomized to continuous subcutaneous infusion FILGRASTIM 10 mcg/kg/day (n = 19), FILGRASTIM 30 mcg/kg/day (n = 10) and no treatment (n = 14) starting the day after marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin's disease and 72% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm3) in the FILGRASTIM-treated groups versus the control group (21.5 days in the control group versus 10 days in the FILGRASTIM-treated groups, p < 0.001). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the FILGRASTIM-treated groups, p < 0.0001).

In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive FILGRASTIM 300 mcg/m2/day (n = 33) or placebo (n = 37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, p < 0.001) and time to recovery of ANC to ≥ 500/mm3 (21 days in the control group and 16 days in the treatment group, p < 0.001).

Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The safety and efficacy of FILGRASTIM to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using FILGRASTIM-mobilized autologous peripheral blood progenitor cells to autologous bone marrow (Study 11). Patients in all these trials underwent a similar mobilization/collection regimen: FILGRASTIM was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of FILGRASTIM ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using FILGRASTIM-mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm3 by day 28. In clinical trials of FILGRASTIM for the mobilization of hematopoietic progenitor cells, FILGRASTIM was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm3) was reached. The rate of engraftment of these cells in the absence of FILGRASTIM post transplantation has not been studied.

Study 11 was a randomized, unblinded study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received FILGRASTIM-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). Patients received daily FILGRASTIM 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin's disease and 43% non-Hodgkin's lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to FILGRASTIM-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs 10 days).

Patients with Severe Chronic Neutropenia

The safety and efficacy of FILGRASTIM to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with severe neutropenia (Study 7).

Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < 500/mm3 on three occasions during a 6-month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < 500/mm^3 per cycle. In addition, patients must have experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4-month observation period followed by FILGRASTIM treatment or immediate FILGRASTIM treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia.

FILGRASTIM was administered subcutaneously. The dose of FILGRASTIM was determined by the category of neutropenia. Initial dose of FILGRASTIM:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

The main efficacy endpoint was response to FILGRASTIM treatment. ANC response from baseline (< 500/mm3) was defined as follows:

- Complete response: median ANC > 1,500/mm3
- Partial response: median ANC ≥ 500/mm3 and ≤ 1,500/mm3 with a minimum increase of 100%
- No response: median ANC < 500/mm3

There were 112 of 123 patients who demonstrated a complete or partial response to FILGRASTIM treatment.

Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving FILGRASTIM of the following parameters:

- incidence of infection
- incidence of fever
- duration of fever
- incidence, duration, and severity of oropharyngeal ulcers
- number of days of antibiotic use

The incidence for each of these 5 clinical parameters was lower in the FILGRASTIM arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although FILGRASTIM substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.

Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Efficacy studies of FILGRASTIM could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting the use of FILGRASTIM for other approved indications

Because of the uncertainty associated with extrapolating animal efficacy data to humans, the selection of human dose for FILGRASTIM is aimed at providing exposures to filgrastim that exceed those observed in animal efficacy studies. The 10 mcg/kg daily dose is selected for humans exposed to myelosuppressive doses of radiation because the exposure associated with such a dose is expected to exceed the exposure associated with a 10 mcg/kg dose in non-human primates. The safety of FILGRASTIM at a daily dose of 10 mcg/kg has been assessed on the basis of clinical experience in approved indications.

The efficacy of FILGRASTIM was studied in a randomized, blinded, placebo-controlled study in a non-human primate model of radiation injury. The planned sample size was 62 animals, but the study was stopped at the interim analysis with 46 animals because efficacy was established. Rhesus macaques were randomized to a control (n = 22) or treated (n = 24) group. Animals were exposed to total body irradiation of 7.4 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Starting on day 1 after irradiation, animals received daily subcutaneous injections of placebo (5% dextrose in water) or filgrastim (10 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC ≥ 1,000/mm3 for 3 consecutive days, or ANC ≥ 10,000/mm3 for more than 2 consecutive days within study day 1 to 5, or ANC ≥ 10,000/mm3 any time after study day 5. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Filgrastim significantly (at 0.023 level of significance) reduced 60-day mortality in the irradiated non-human primates: 21% mortality (5/24) in the filgrastim group compared to 59% mortality (13/22) in the control group.

PRECLINICAL SAFETY DATA

Filgrastim was studied in repeated dose toxicity studies up to 1 year in duration which revealed changes attributable to the expected pharmacological actions including increases in 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 similar to Filgrastim, 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.

PRESENTATION

Nexfil 300mcg Injection is available as: 0.5ml x 1 PFS.

STORAGE INSTRUCTIONS

Store between 2 - 8°C, protect from light.

- Do not freeze and avoid shaking.

- Keep all medicines out of sight and reach of children.

-Injection should not be used if the seal is broken,

the liquid is colored or any particle is found.

REGISTRATION NUMBER

Nexfil 300mcg Injection: 077534

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

Nextar Pharma (Pvt.) Ltd.

E-58, North Western Industrial Zone, Port

Qasim, Karachi - Pakistan.

Marketed by:

The Searle Company Limited,

One IBL Center, 2nd Floor, Plot # 1,

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Off Shahra-e-Faisal, Karachi - Pakistan.

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