StimoFil 300 mcg/0.5 ml, 480 mcg/0.5 ml

PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

StimoFil 300 mcg/0.5 ml
StimoFil 480 mcg/0.5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

StimoFil 300 mcg/0.5 ml:
Each ml of solution contains 60 million units (MU) (equivalent to 600 micrograms [µg]) of (filgrastim).
Each pre-filled syringe contains 30 MU (equivalent to 300 micrograms of filgrastim in 0.5 ml solution for injection or infusion.

StimoFil 480 mcg/0.5 ml:
Each ml of solution contains 96 million units (MU) (equivalent to 960 micrograms [µg]) of filgrastim.
Each pre-filled syringe contains 48 MU (equivalent to 480 micrograms of filgrastim in 0.5 ml solution for injection or infusion.

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

Excipient with known effect:

Each ml of solution contains 50 mg of D-sorbitol

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

StimoFil 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 StimoFil are similar in adults and children receiving cytotoxic chemotherapy.

StimoFil 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 StimoFil is indicated to increase neutrophil counts and to reduce the incidence and

duration of infection-related events.

StimoFil 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

StimoFil therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Posology

Established cytotoxic chemotherapy

The recommended dose of filgrastim is 0.5 MU/kg/day (5 micrograms/kg/day). The first dose of StimoFil should not be administered less than 24 hours following cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 microgram/m^2/day (4.0 to 8.4 microgram/kg/day) was used.

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

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

In patients treated with myeloablative therapy followed by bone marrow transplantation

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

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

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

ANC = absolute neutrophil count

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

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU (10 µg)/kg/day for 5-7 consecutive days. 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 $< 0.5 \times 10^9$/L to $> 5.0 \times 10^9$/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukaphereses are recommended.

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

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

In patients with severe chronic neutropenia (SCN)

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

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

Dose adjustments: Filgrastim should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than 1.5×10^9/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.

In patients with HIV infection

For reversal of neutropenia:

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

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

For maintenance of normal neutrophil counts:

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

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 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.

Method of administration

Established cytotoxic chemotherapy

Filgrastim may be administered as a daily subcutaneous injection or alternatively as a daily intravenous infusion diluted in glucose 50 mg/ml (5%) solution over 30 minutes. For further instructions on dilution prior to infusion see section 6.6. The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance.

Patients treated with myeloablative therapy followed by bone marrow transplantation

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

In patients with Mobilisation of PBPC

Filgrastim for PBPC mobilisation when used alone:

Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions filgrastim should be diluted in 20 ml of 5% glucose solution (see section 6.6).

Filgrastim for PBPC mobilisation after myelosuppressive chemotherapy:

Filgrastim should be given by subcutaneous injection.

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

Filgrastim should be given by subcutaneous injection.

In patients with SCN

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

In patients with HIV infection

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Special warnings 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 $< 100 \times 10^9$/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets $< 50 \times 10^9$/L were reported and attributed to the leukapheresis procedure. If more than one leukapheresis is required, particular attention should be paid to donors with platelets $< 100 \times 10^9$/L prior to leukapheresis; in general apheresis should not be performed if platelets are $< 75 \times 10^9$/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 $> 70 \times 10^9$/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

StimoFil contains D-sorbitol as an excipient at a concentration of 50 mg/ml. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product. [4]

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

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 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.

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**
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	Hyperuricaemia Blood uric acid	Blood glucose decreased Pseudogout[a] (Chondrocalcino		

MedDRA system organ class	Adverse reactions					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
		dehydrogenase increased	increased	sis Pyrophosphate) Fluid volume disturbances		
Nervous system disorders	Headache[a]	Dizziness, Hypoaesthesia, Paraesthesia				
Vascular Disorders		Hypotension Hypertension	Veno-occlusive disease[d]	Capillary leak syndrome[a] ,Aortitis		
Psychiatric disorders		Insomnia				
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			

MedDRA system organ class	Adverse reactions					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
			increased			
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Rash maculopapular	Sweets syndrome (acute febrile neutrophilic dermatosis) Cutaneous vasculitis[a]		
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[c]	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis		
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Urine abnormality Glomerulonephritis		
General disorders and administration site conditions	Fatigue[a] Mucosal inflammation[a] Pyrexia	Chest pain[a] Asthenia[a] Pain[a] Malaise[e] Oedema peripheral[e]	Injection site reaction			
Injury, poisoning and procedural complications		Transfusion reaction[e]				
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection				

[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 StimoFil use in geriatic subjects for other approved StimoFil 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

The effects of StimoFil 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: cytokines, ATC code: L03AA02

StimoFil is a biosimilar medicinal product that has been demonstrated to be similar in quality, safety and efficacy to the reference medicinal product Neupogen. More Detailed information is available on the website of the Ministry of Health http://www.health.gov.il/hozer/dr_127.pdf

Pharmacodynamic effects

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

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

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates haematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions. Recipients of allogeneic PBPCs mobilised with filgrastim experienced significantly more rapid haematological recovery, leading to a significant decrease in time to unsupported platelet recovery when compared with allogeneic bone marrow transplantation.

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

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

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

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

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

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

In normal donors, a 10 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 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

Absorption

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

Distribution

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

Elimination

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous 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 StimoFil 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 10 ng/ml for 8 to 16 hours. The volume of distribution in blood is approximately 150 ml/kg.

5.3 Preclinical safety data

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

D-Sorbitol
Glacial Acetic acid
Sodium hydroxide
Polysorbate 80
Water for injection

6.2 Incompatibilities

StimoFil must not be diluted with saline solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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 StimoFil. If exposure has been greater than 24 hours or frozen more than once then StimoFil 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

Pre-filled syringe with injection needle, with a needle safety guard. Package containing 1, 3, 5 or 10 pre-filled syringe (s) with blister. The pre-filled syringes are made from Type I glass with a permanently attached stainless steel needle in the tip and have 1/40 printed markings for graduations from 0.1 mL to 1 mL on the barrel. The needle cover of the pre-filled syringe contains dry natural rubber (see section 4.4). Each pre-filled syringe contains 0.5 ml solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If required, StimoFil 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.

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

When diluted in 5% glucose, StimoFil 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.

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

7. NAME AND ADDRESS OF THE MANUFACTURER

Intas pharmaceuticals Ltd., Gujarat, India

8. NAME AND ADDRESS OF THE REGISTRATION HOLDER

Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Kiryat Matalon, Petach-Tikva.

9. MARKETING AUTHORISATION NUMBERS

StimoFil 300 mcg/0.5 ml: 164-19-36445-00
StimoFil 480 mcg/0.5 ml: 164-20-36446-00

The leaflet format has been determined by the Ministry of Health, and the content has been checked and approved in November 2019