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

StimoFil is a biosimilar medicinal product that has been demonstrated to be similar in quality, safety and efficacy to the reference medicinal product Neupogen. Please be aware of any differences in the indications between the biosimilar medicinal product and the reference medicinal product. Information regarding biosimilar products can be found on the website of the Ministry of Health: https://www.gov.il/he/Departments/General/biosimilar

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 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 StimoFil are similar in adults and children receiving cytotoxic chemotherapy.

StimoFil 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 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 1.0×10^9/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 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

Posology
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 tumors, lymphomas, and lymphoid leukemias, 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 1-2 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**
> 1.0×10^9/L for 3 consecutive days	Reduce to 0.5 MU (5 µg) /kg/day
Then, if ANC remains > 1.0×10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0×10^9/L during the treatment period, the dose of filgrastim should be	

re-escalated according to the above steps

ANC = absolute neutrophil count

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

For PBPC mobilization 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 $\leq$ 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.

Special populations

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

Pediatric 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 pediatric 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.

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 Mobilization of PBPC
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 (see section 6.6).

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
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

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Special warnings 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 dyspnea 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 granulocytecolonystimulating factor administration, and is characterised by hypotension, hypoalbuminaemia, edema 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).

Splenomegaly and splenic rupture

Generally asymptomatic cases of splenomegaly and 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 leukemia
The safety and efficacy of filgrastim administration in patients with myelodysplastic syndrome or chronic myelogenous leukemia 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 leukemia from acute myeloid leukemia.

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

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

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

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

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

<u>Special warnings and precautions associated with co-morbidities</u>

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 tumor 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 anemia 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 anemia. Regular monitoring of platelet count and hematocrit 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 mobilized PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

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

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

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 hematopoietic 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
There are no prospectively randomised comparisons of the two recommended mobilization 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 mobilization 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 mobilization of PBPC to achieve the recommended minimum yield ($\geq 2.0 \times 10^6$ $CD34^+$ cells/kg) or acceleration of platelet recovery to the same degree.

Some cytotoxic agents exhibit particular toxicities to the hematopoietic progenitor pool and may adversely affect progenitor mobilization . Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilization , may reduce progenitor yield. However, the administration of melphalan, carboplatin or carmustine (BCNU) together with filgrastim has been shown to be effective for progenitor mobilization . 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 mobilized in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

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

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

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

<u>Special precautions in normal donors undergoing peripheral blood progenitor cell mobilization</u>

Mobilization 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 mobilization should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to h
ematological values and infectious diseases.

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

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

If more than one leukapheresis is required, particular attention should be paid to donors with platelets

< 100 x 10^9/L prior to leukapheresis; in general apheresis should not be performed if platelets are < 75 x 10^9/L.

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

Special precautions in recipients of allogeneic PBPC mobilized 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 leukemia or have evidence of leukemic evolution.

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

Transformation to leukemia or myelodysplastic syndrome
Special care should be taken in the diagnosis of SCNs to distinguish them from other hematopoietic disorders such as aplastic anemia, myelodysplasia and myeloid leukemia. 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 leukemia in clinical trial patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukemias 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 leukemic 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.

Hematuria 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

Blood cell counts
Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice 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 anemia 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 anemia. Regular monitoring of blood counts is recommended (see above).

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

All patients

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

StimoFil contains D-sorbitol as an excipient at a concentration of 50 mg/ml. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be lifethreatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.
A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

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

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 hematopoietic 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 amount of data from the use of filgrastim in pregnant women. Studies in

animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3). There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.
Filgrastim is not recommended during pregnancy.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

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 leukemia 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), anemia, 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 (≥ 1/1,000 to < 1/100)**	**Rare (1/10,000 to < 1/1,000)**
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection		

MedDRA system organ class	Adverse reactions			
	Very common (≥1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (1/10,000 to < 1/1,000)**
Blood and lymphatic system disorders	Thrombocytopenia Anemia[e]	Splenomegaly[a] Haemoglobin decreased[e]	Leukocytosis[a]	Splenic rupture[a] Sickle cell anemia 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		Hypotension Hypertension	Veno-occlusive disease[d]	Capillary leak syndrome[a] Aortitis
Respiratory, thoracic and mediastinal disorders		Haemoptysis Dyspnoea Cough[a] Oropharyngeal pain[a,e] Epistaxis	Acute respiratory distress syndrome[a] Respiratory failure[a] Pulmonary edema[a] Pulmonary hemorrhage 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	

MedDRA system organ class	Adverse reactions			
	Very common (≥1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (1/10,000 to < 1/1,000)**
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Rash maculopapular	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] Edema 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, angiedema, 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 edema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4).

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

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

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 (see section 4.4).

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

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

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).

d. Pediatric population

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 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 pediatric 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 StimoFil use in geriatric subjects for other approved StimoFil indications.

Pediatric SCN patients
Cases of decreased bone density and osteoporosis have been reported in pediatric 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: immunostimulants, colony stimulating factors, ATC code: L03AA02

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 hospitalization after induction chemotherapy for acute myelogenous leukemia 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, mobilizes hematopoietic progenitor cells into the peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates hematopoietic recovery reducing the duration of risk for haemorrhagic complications and the need for platelet transfusions.

Recipients of allogeneic PBPCs mobilized with filgrastim experienced significantly more rapid hematological 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 leukemias 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 leukemias, 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 mobilization of PBPCs in normal donors prior to allogeneic PBPC transplantation

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

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

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

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Elimination

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

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 sodium chloride solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

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

6.3 Shelf life

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.

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

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger rod and push firmly at the end of the injection to ensure that syringe emptying is completed. Hold the skin securely until the injection is completed. Keep the syringe still and slowly lift your thumb from the plunger rod head. The plunger rod will move up with your thumb and the spring retracts the needle from the site, into the Needle safety guard.
Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

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

Revised in December 2023 according to MoH guidelines.