NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Nivestim® 120 micrograms filgrastim in 0.2 mL, or 300 micrograms or 480 micrograms filgrastim in 0.5 mL Solution for Injection/Infusion (prefilled syringes).

Nivestim is a biosimilar product. The prescribing physician should be involved in any decision regarding its interchangeability (refer to http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp). Nonclinical and clinical comparability studies using Nivestim and Neupogen® are described in the Pharmacological Properties section of this datasheet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prefilled syringe of Nivestim contains 120 µg (equivalent to 12 million units) in 0.2 mL of solution for injection; or, 300 µg (equivalent to 30 million units) or 480 µg (equivalent to 48 million units) of filgrastim in 0.5 mL of solution for injection.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection/Infusion (prefilled syringes).

Nivestim is a sterile, clear, colourless solution, practically free from particles, for subcutaneous (SC) or intravenous (IV) injection or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Established Cytotoxic Chemotherapy

Nivestim is indicated for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia and its clinical sequelae in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

Peripheral Blood Progenitor Cell Mobilisation (PBPC)

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

Severe Chronic Neutropenia (SCN)

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

HIV Infection

Nivestim is indicated for the treatment of persistent neutropenia (ANC ≤ 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 Dose and method of administration

Nivestim 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.

Dose

Established Cytotoxic Chemotherapy

The recommended dose of filgrastim is 5 µg/kg/day. The first dose of filgrastim should not be administered less than 24 hours following cytotoxic chemotherapy. Filgrastim may be given as a daily subcutaneous (SC) injection or as a daily intravenous (IV) infusion diluted in 5% glucose solution given over 30 minutes (see section 6.6, Instructions for dilution). The SC route is preferred in most cases. There is some evidence from a study of single dose administration that IV 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 circumstances.

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 leukaemia, 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 to 2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of filgrastim therapy, prior to the time of the expected neutrophil nadir, is not recommended.

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of filgrastim is 10 µg/kg/day given as a 30 minute or 24 hour IV infusion or 10 µg/kg/day given by continuous 24 hour SC infusion. Filgrastim should be diluted in 20 mL of 5% glucose solution (see section 6.6, Instructions for dilution). The first dose of filgrastim should not be administered less than 24 hours following cytotoxic chemotherapy but within 24 hours of bone marrow infusion.

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

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

Neutrophil Count	**Dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 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

Peripheral Blood Progenitor Cell Mobilisation

Mobilisation of PBPC in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation with or without bone marrow transplantation

The recommended dose of filgrastim for PBPC mobilisation when used alone is 10 µg/kg/day as a 24 hour SC continuous infusion or a single daily SC injection for 5 to 7 consecutive days. For infusions, filgrastim should be diluted in 20 mL of 5% glucose solution (see section 6.6, Instructions for dilution). Timing of leukapheresis: one or two leukaphereses on days 5 and 6 are often sufficient. In other circumstances, additional leukapheresis may be necessary. Filgrastim dosing should be maintained until the last leukapheresis.

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

Mobilisation of PBPC in normal donors prior to allogeneic PBPC transplantation

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

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

Severe Chronic Neutropenia (SCN)

Congenital neutropenia

The recommended starting dose is 12 µg/kg/day SC as a single dose or in divided doses.

Idiopathic or cyclic neutropenia

The recommended starting dose is 5 µg/kg/day SC as a single dose or in divided doses.

Dose adjustments

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

HIV Infection

For reversal of neutropenia

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

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

For maintaining normal neutrophil counts

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

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 dosage recommendations cannot be made.

Paediatric population

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

Renal or hepatic impairment

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

4.3 Contraindications

Filgrastim should not be administered to patients with known hypersensitivity to filgrastim or to any of the excipients.

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 (Kostmann's syndrome) with abnormal cytogenetics (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

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.

Splenic rupture and splenomegaly

Generally asymptomatic cases of splenomegaly and cases of splenic rupture have been reported in patients and normal donors following administration of filgrastim. Some of these cases were fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture or enlarged spleen should be considered in donors reporting left upper abdominal pain 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.

Sickle cell crisis

Publications in the literature have reported that high leukocyte counts are disadvantageous prognostic factors in patients with sickle cell disease. Therefore, clinicians should exercise caution when administering filgrastim in patients with sickle cell trait or sickle cell disease, should institute close monitoring of appropriate clinical parameters and laboratory status and be attentive of the possible association of filgrastim with splenic enlargement and vaso-occlusive crisis.

Sickle cell anaemia with crisis, 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.

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 $< 100 \times 10^9$/L).

Capillary leak syndrome

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after G-CSF administration, and is characterised by hypotension, hypoalbuminemia, oedema and haemoconcentration. 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.

Bone imaging

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

Myeloid progenitors

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 (such as those treated with extensive radiotherapy or chemotherapy or those with bone marrow infiltration by tumour), neutrophil response may be diminished.

Graft versus host disease

The effect of filgrastim on Graft versus Host Disease (GvHD) has not been defined.

Pulmonary adverse effects

Pulmonary adverse effects, in particular interstitial lung disease, 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 of acute respiratory distress syndrome (ARDS). Nivestim should be immediately 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.

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML) in Breast Cancer and Lung Cancer Patients

In the post-marketing observational study setting, MDS and AML have been associated with the use of filgrastim in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. Monitor patients for signs and symptoms of MDS/AML in these settings. There has been limited association between the occurrence of MDS and AML and the use of filgrastim in conjunction with chemotherapy and/or radiotherapy in breast cancer patients.

Aortitis

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced include 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.

Excipients

Nivestim contains sorbitol (E420). Patients with rare heredity 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 HFI. Medicines (containing sorbitol/fructose) given intravenously may be life-threatening 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.

Nivestim contains less than 1 mmol sodium (23 mg) per 0.6 mg/mL or 0.96 mg/mL dose, that is to say essentially sodium-free.

Malignant cell growth

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

Myelodysplastic syndrome or chronic myeloid leukaemia

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

Special precautions in patients receiving cytotoxic chemotherapy

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 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, neurological and dermatological effects (please refer to the prescribing information of the specific chemotherapy agents used).

Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Because of the potential of receiving higher doses of chemotherapy (e.g. full doses of 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 PBPC has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Special precautions in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

Mobilisation

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

Prior exposure to cytotoxic agents

Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield ($\geq 2.0 \times 10^6$ $CD34^+$ cells/kg) or acceleration of platelet recovery, to the same degree.

Some cytotoxic agents exhibit particular toxicities to the haematopoietic progenitor pool and may adversely affect progenitor mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor mobilisation, may reduce progenitor yield. However, the administration of melphalan, carboplatin or BCNU together with filgrastim has been shown to be effective for progenitor mobilisation. When a peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment, not requiring progenitor support, should be considered.

Assessment of progenitor cell yields

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

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

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

Special precautions in normal donors undergoing PBPC mobilisation prior to allogeneic PBPC transplantation

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

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

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

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

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

Filgrastim administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

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

Special precautions in recipients of allogeneic PBPCs mobilised with filgrastim

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

Special precautions in patients with Severe Chronic Neutropenia (SCN)

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

Transformation to leukaemia or myelodysplastic syndrome (MDS)

Special care should be taken in the diagnosis of SCN to distinguish it 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 or leukaemia in clinical trial patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia (Kostmann's syndrome). 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 were 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 occur. It is currently unclear whether long-term treatment of patients with severe chronic neutropenia will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients with Kostmann's syndrome at regular intervals (approximately every 12 months).

Blood cell counts

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.

Others

Causes of transient neutropenia, such as viral infections, should be excluded. Splenic enlargement is a direct effect of treatment with filgrastim. 31% of patients with SCN in studies were documented as having palpable splenomegaly. Increases in volume, measured radiographically, occurred early during filgrastim therapy and tended to plateau. 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/proteinuria occurred in a small number of patients. Regular urinanalysis 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

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

Risk associated with increased doses of myelosuppressive medications

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

Laboratory monitoring

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Considering all sources of data on immunogenicity, rates of generation of antibodies against filgrastim are generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity or adverse clinical consequences at present.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to filgrastim with the incidence of antibodies to other products may be misleading.

Laboratory tests

Monitoring of Complete Blood Count (CBC) during filgrastim therapy is recommended.

Paediatric population

Established cytotoxic chemotherapy

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

In patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

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

In patients with SCN

The safety and efficacy in neonates have not been established. Long term administration of filgrastim is indicated in children with severe congenital, cyclic or idiopathic neutropenia with an ANC $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Paediatric use in the SCN and cancer settings

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

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.

Elderly population

In patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

The safety and efficacy of filgrastim have not been assessed in normal donors > 60 years of age.

4.5 Interaction with other medicines and other forms of interaction

Cytotoxic chemotherapy

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.

Lithium

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

Bone imaging

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

4.6 Fertility, pregnancy and lactation

Pregnancy – Category B3

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

Lactation

It is not known whether filgrastim is secreted in human milk. Filgrastim is not recommended for use in nursing women.

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 machinery

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

4.8 Undesirable effects

Summary of safety profile

Bone pain and pain in extremity occurred at a higher incidence in filgrastim-treated patients as compared with placebo-treated patients across all indications.

Administration of filgrastim at the recommended dosage is frequently associated with musculoskeletal pain specifically in medullar bones. This is usually mild or moderate (10%), but occasionally severe (3%), and is generally controlled with standard analgesics.

In combined clinical trial data involving a total of 5004 patients, adverse reactions are listed below. Adverse reactions observed in the combined clinical trial data which are present in the adverse reaction tables by indication below, are not included in this list:

Very common (≥ 1/10): nausea, vomiting, pyrexia, fatigue, and headache.

Common (≥ 1/100 and < 1/10): hypertension, pain, oral pain, oropharyngeal pain, haemoptysis, chest pain, back pain, arthralgia, malaise, cough, oedema peripheral, decreased appetite, constipation, sepsis, bronchitis, upper respiratory tract infection, urinary tract infection, muscle spasms, dizziness, hypoaesthesia, paraesthesia, insomnia, erythema and transfusion reaction.

Uncommon (≥ 1/1,000 and < 1/100): hypersensitivity, lung infiltration and rash maculo-papular.

Rare (≥ 1/10,000 and < 1/1,000): glomerulonephritis, extramedullary haemotopoiesis.

In normal donors undergoing PBPC mobilisation the most commonly reported undesirable effect was mild to moderate transient musculoskeletal pain.

In patients with SCN, the most frequent clinical adverse events attributed to filgrastim were bone pain and general musculoskeletal pain. Undesirable effects related to filgrastim therapy in SCN patients have been reported and for some their frequency tends to decrease with time.

In clinical studies in patients with HIV, the only undesirable effects that were consistently considered to be related to filgrastim administration were musculoskeletal pain, predominantly mild to moderate bone pain and myalgia. The incidence of these events was similar to that reported in cancer patients.

Tabulated list of adverse reactions

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

Cancer patients

System Organ Class	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)
Immune system disorder					Allergic reaction
Metabolic and nutrition disorders		Anorexia			
Nervous system disorders		Headache			
Respiratory disorders		Cough Pharyngolaryngeal pain			Lung infiltration
Gastrointestinal disorders	Nausea Vomiting	Constipation Diarrhoea			
Skin and subcutaneous disorders		Alopecia Rash			Acute febrile neutrophilic dermatosis Cutaneous vasculitis
Musculoskeletal disorders		Chest pain Musculoskeletal pain			Rheumatoid arthritis exacerbation
Renal and urinary disorders					Urinary abnormalities
General disorders and administration site condition		Fatigue Asthenia Mucosal inflammation	Pain		
Investigations	Blood gamma-glutamyl-transferase (GGT) increased Blood alkaline phosphatase increased Blood lactate dehydrogenase increased Blood uric acid increased				

Normal donors undergoing PBPC mobilisation

System Organ Class	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)
Blood and lymphatic system disorders	Leukocytosis Thrombocytopenia	Splenomegaly	Spleen disorder		

System Organ Class	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)
Immune system disorder			Severe allergic reaction		
Metabolic and nutrition disorders			Hyperuricaemia		
Nervous system disorders	Headache				
Respiratory disorders					Haemoptysis Lung infiltration
Musculoskeletal disorders	Musculoskeletal pain				Rheumatoid arthritis exacerbation
Investigations		Blood alkaline phosphatase increased Blood lactate dehydrogenase increased	Serum glutamic-oxaloacetic transaminase (SGOT) increased		

Patients with SCN

System Organ Class	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)
Blood and lymphatic system disorders	Anaemia Splenomegaly	Thrombocytopenia	Spleen disorders		
Metabolic and nutrition disorders	Hyperuricaemia				
Nervous system disorders		Headache			
Gastrointestinal disorders		Diarrhoea			
Hepatobiliary disorders		Hepatomegaly			
Skin and subcutaneous disorders		Alopecia Rash Cutaneous vasculitis			
Musculoskeletal disorders	Musculoskeletal pain	Osteoporosis			
Renal and urinary disorders			Haematuria Proteinuria		
General disorders and administration site condition		Injection site pain			

System Organ Class	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)
Investigations	Decreased glucose Blood alkaline phosphatase increased Blood lactate dehydrogenase increased				

Patients with HIV

System Organ Class	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)
Blood and lymphatic system disorders		Splenomegaly			
Musculoskeletal disorders	Bone pain Musculoskeletal pain Myalgia				

Adverse reactions from spontaneous reporting

Cases of pulmonary haemorrhage and haemoptysis have been reported in patients receiving filgrastim.

Cases of aortitis have been reported in patients receiving filgrastim.

Cases of myelodysplastic syndrome and acute myeloid leukaemia have been reported in breast and lung cancer patients receiving filgrastim in conjunction with chemotherapy and/or radiotherapy. Events of pseudogout have been reported very rarely (estimated 0.03 cases per 100,000 exposures [0.00003%]) in patients with cancer treated with filgrastim.

Cases of decreased bone density and osteoporosis have been reported commonly (≥ 1/100 to < 1/10) in paediatric patients with SCN receiving chronic treatment with filgrastim.

Cases of extramedullary haematopoiesis have been reported rarely (≥ 1/10,000 and < 1/1,000) in patients receiving filgrastim.

Description of selected adverse reactions

Allergic reactions

Allergic-type reactions, including anaphylactic reactions, rash, and urticaria, occurring on initial or subsequent treatment have been reported in patients receiving filgrastim; approximately half of these were associated with the initial dose. Overall, reports were more common after IV administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship.

Allergic-type reactions to filgrastim have rarely been reported in post marketing experience. Symptoms suggestive of severe allergic reactions have been reported very rarely in normal donors.

Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Cutaneous vasculitis

Very rare events of cutaneous vasculitis have been reported in cancer patients treated with filgrastim. During long-term use, cutaneous vasculitis has been reported in 2% of SCN patients. The mechanism of vasculitis in patients receiving filgrastim is unknown.

Respiratory disorders

Rare pulmonary adverse effects including interstitial pneumonia, pulmonary oedema, and lung infiltration have been reported in patients with cancer following administration of filgrastim, some cases with an outcome of respiratory failure or ARDS, which may be fatal.

For allogeneic (also called normal or healthy) donors, pulmonary adverse events (haemoptysis, lung infiltration) have been very rarely reported (< 0.01%).

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).

Common, but generally asymptomatic, cases of splenomegaly have been reported in normal donors undergoing PBPC mobilisation.

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

Splenomegaly, which may be progressive in a minority of cases, has also been reported in SCN patients.

Sickle cell anaemia

Isolated cases of sickle cell anaemia with crisis, in some cases fatal, have been reported in patients with sickle cell disease.

Exacerbation of rheumatoid arthritis

Exacerbation of rheumatoid arthritis has been observed in individual cases in patients with cancer and normal donors.

Investigations

Reversible, dose-dependent and usually mild-to-moderate increases in blood uric acid, blood alkaline phosphatase, blood lactate dehydrogenase and gamma-glutamyl transpeptidase (GGT), with no associated clinical effects, have been seen in patients receiving filgrastim after cytotoxic chemotherapy.

Transient, minor increases in blood alkaline phosphatase, blood lactate dehydrogenase, serum glutamic-oxaloacetic transaminase (SGOT) and blood uric acid have been reported in normal donors receiving filgrastim; these were without clinical sequelae.

In SCN patients transient increases with no clinical symptoms were observed in blood uric acid, blood lactate dehydrogenase and blood alkaline phosphatase. Transient, moderate decreases in non-fasting blood glucose have also been seen.

Adverse reactions in cancer patients

In clinical trials in cancer patients, filgrastim did not increase the incidence of clinical undesirable effects associated with cytotoxic chemotherapy. Undesirable effects reported with equal frequency in patients treated with filgrastim/chemotherapy and placebo/chemotherapy included nausea and vomiting, alopecia, diarrhoea, fatigue, anorexia, mucositis, headache, cough, rash, chest pain, asthenia, oral pain, constipation and pain. Less frequent adverse events include urinary abnormalities (predominantly mild or moderate dysuria). Transient decreases in blood pressure, not requiring clinical treatment, have been reported occasionally.

Vascular disorders (e.g. veno-occlusive disease and fluid volume disturbances) have been reported occasionally in patients undergoing high dose chemotherapy followed by autologous bone marrow transplantation. The causal association with filgrastim has not been established.

Adverse reactions in PBPC mobilisation in normal donors

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

Adverse reactions in SCN patients

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

Headache and diarrhoea have been reported shortly after starting filgrastim therapy, typically in less than 10% of patients. Thrombocytopenia, anaemia and epistaxis have also been reported. There have been very few instances of proteinuria/haematuria.

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.

Sweets syndrome

The occurrence of Sweets syndrome (acute febrile neutrophilic dermatosis) has been reported in patients treated with filgrastim.

GvHD

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

The effects of filgrastim overdose have not been established.

Doses up to 138 µg/kg/day were administered to patients in Bone Marrow Transplant (BMT) studies without toxic effects.

Discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within one to two days, with a return to normal levels in one to seven days.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

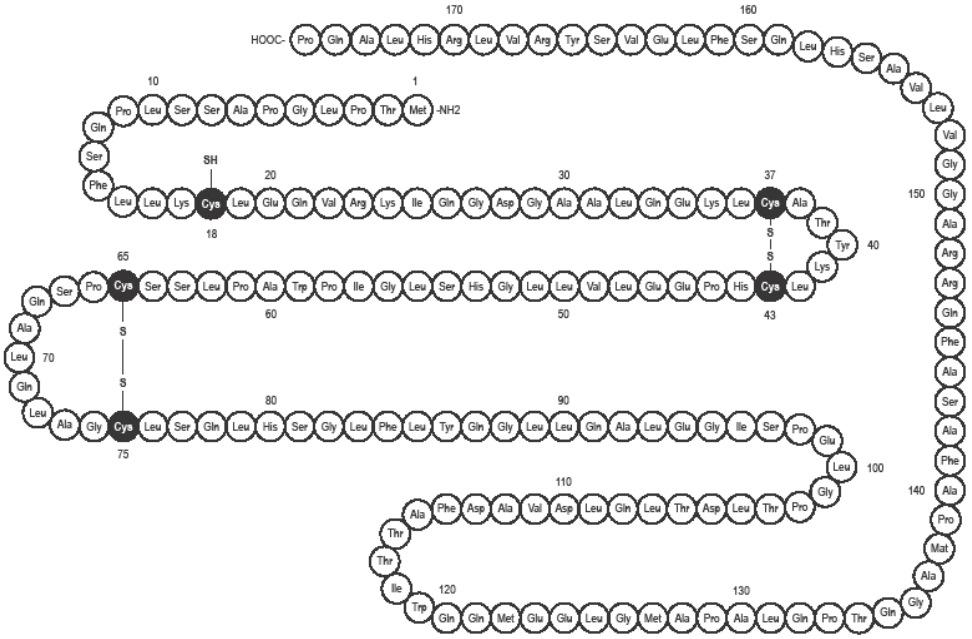
Pharmacotherapeutic group: Granulocyte colony-stimulating factors, leukocyte growth factor, immunostimulants

ATC code: L03AA02

Filgrastim (recombinant-methionyl human granulocyte colony-stimulating factor, r-metHuG-CSF, from *E. coli*).

Filgrastim is a highly purified non-glycosylated protein comprising 175 amino acids. Filgrastim is produced in a laboratory strain of *Escherichia coli* bacteria which has been genetically altered by the addition of a gene for the granulocyte colony-stimulating factor.

A schematic diagram of the amino acid sequence is provided below:



Molecular formula: $C_{845}H_{1339}N_{223}O_{243}S_9$

Molecular weight: 18800 Da

CAS Number: 121181-53-1

Mechanism of action

Human granulocyte colony-stimulating factor is a glycoprotein, which regulates the production and release of functional neutrophils from the bone marrow. Nivestim, containing r-metHuG-CSF (filgrastim), causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes. In some severe chronic neutropenia patients filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment.

Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced by the human body in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within one to two days, and to normal levels within one to seven days.

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

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

Use of filgrastim, either alone, or after chemotherapy, mobilises haematopoietic progenitor cells into 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 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.

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 haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells.

Comparability of Nivestim with Neupogen

Nivestim and Neupogen have been demonstrated to be pharmacodynamically equivalent *in vivo* and in healthy volunteers.

An *in vivo* study compared the efficacy of Nivestim and Neupogen using a cyclophosphamide (CPA)-induced neutropenic model in male rats. Nivestim and Neupogen induced a comparable neutrophilic pharmacodynamic response following daily subcutaneous injections of 30 µg/kg/dose or 100 µg/kg/dose for 4 days. In a 28-day repeat-dose toxicity study Nivestim and Neupogen demonstrated comparable statistically significant dose-dependent increases in the number of circulating neutrophils.

Pharmacodynamic properties of Nivestim and Neupogen were compared in a single-dose Phase I study in healthy volunteers. Intravenous and subcutaneous administration of single 10 µg/kg doses provided similar ANC values.

	Mean ANC $AUC_{0\text{-tlast}}$, 10^9.h/L			
Dose Group	Nivestim	Neupogen	Ratio	90% CI
10 µg/kg IV (n=19)	1209.32	1164.04	1.03	0.99 – 1.08*
10 µg/kg SC (n=26)	1334.48	1299.75	1.03	0.99 – 1.06*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Pharmacodynamic properties of Nivestim and Neupogen were also compared in a multiple-dose Phase I study in healthy volunteers. Subcutaneous administration of multiple (five) 5 µg/kg and 10 µg/kg doses provided similar ANC $AUC_{0\text{-tlast}}$ and $CD34^+$ values.

Dose Group	Mean ANC $AUC_{0\text{-tlast}}$, 10^9.h/L		Ratio	90% CI
	Nivestim	Neupogen		
5 µg/kg (n=24)	1632.96	1659.83	0.98	0.92 – 1.05*
10 µg/kg (n=23)	2170.39	2249.50	0.97	0.93 – 1.01*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Dose Group	Mean $CD34^+$ count, cells/µL (range)		Ratio	90% CI
	Nivestim	Neupogen		
5 µg/kg (n=24)	47.2 (14.0 – 158.0)	46.0 (12.0 – 187.0)	1.03	0.85 – 1.24*
10 µg/kg (n=23)	81.9 (19 – 184)	77.5 (28 – 232)	1.06	0.90 – 1.24*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Therapeutic equivalence of Nivestim and Neupogen was demonstrated in a double-blind, randomised, controlled Phase 3 trial of patients receiving doxorubicin and docetaxel as combination therapy for invasive breast cancer. 279 patients were randomised (2:1) to 5 µg/kg Nivestim (n = 184) or 5 µg/kg Neupogen (n = 95). Up to six cycles of treatment were administered at 3-weekly intervals.

The mean duration of severe neutropenia (DSN) (ANC < 0.5 x 10^9/L) in Cycle 1 was 1.6 days in the Nivestim group compared with 1.3 days in the Neupogen group. The 90%CI for the difference of the treatment means lies within the pre-defined range -1 to +1 day. Analysis of DSN in Cycle 1 gave adjusted means (adjusted for treatment setting) of 1.85 days (95% CI 1.63 – 2.08) for Nivestim and 1.47 days (95% CI 1.19 – 1.75) for Neupogen, with a difference between the two treatment groups means of 0.38 (95% CI 0.08 – 0.68).

In subjects with severe neutropenia, the majority (93.3%) of subjects in the Nivestim group and all (100%) subjects in the Neupogen group had a DSN of less than 3 days. Eleven subjects (6.7%) in the Nivestim group had a DSN of 4 or 5 days: 10 (6.1%) had a DSN of 4 days and 1 (0.8%) had a DSN of 5 days. Of the 10 subjects in the Nivestim group with a DSN of 4 days, two had febrile neutropenia (ANC < 0.5 x 10^9/L and body temperature ≥ 38.5°C) in the same cycle. The one subject with a DSN of 5 days also had febrile neutropenia in the same cycle.

Time to ANC Recovery (ANC > 3 x 10^9/L) was similar in both treatment groups. Mean time to ANC recovery in Cycle 1 was 7.8 days in both the Nivestim and Neupogen groups; in Cycles 2 and 3, mean time to ANC recovery was 7.4 days and 7.5 days for the Nivestim group and 7.6 days in both cycles for the Neupogen group.

5.2 Pharmacokinetic properties

Absorption

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

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

Distribution

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

Elimination

Continuous infusion with filgrastim over a period of up to 28 days, in patients recovering from autologous bone-marrow transplantation, resulted in no evidence of filgrastim accumulation and comparable elimination half-lives.

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

Comparability of Nivestim with Neupogen

Equivalent pharmacokinetic (PK) profiles of Nivestim and Neupogen have been demonstrated in healthy volunteers in a single-dose Phase I study and a multiple-dose Phase I study.

Mean values for $AUC_{0–tlast}$ and C_{max} were similar between treatment groups following intravenous and subcutaneous administration of single 10 µg/kg doses of Nivestim and Neupogen.

	Mean $AUC_{0-tlast}$, pg.h/mL			
Dose Group	Nivestim	Neupogen	Ratio	90% CI
10 µg/kg IV (n=20)	987787.82	973891.60	1.01	0.93 – 1.09*
10 µg/kg SC (n=26)	676926.90	654492.44	1.03	0.94 – 1.14*

* Predefined range of 0.80 – 1.25 for concluding equivalence

	Mean C_{max}, pg/mL			
Dose Group	Nivestim	Neupogen	Ratio	90% CI
10 µg/kg IV (n=20)	249871.93	240007.94	1.04	0.92 – 1.17*
10 µg/kg SC (n=26)	74070.64	71012.21	1.04	0.94 – 1.16*

* Predefined range of 0.80 – 1.25 for concluding equivalence

PK parameters in the multiple-dose study were assessed as secondary endpoints. Mean values for $AUC_{0–tlast}$ and C_{max} following multiple (five) subcutaneous 5 µg/kg and 10 µg/kg doses of Nivestim and Neupogen were as follows.

Dose Group	Mean $AUC_{0\text{-}tlast}$, pg.h/mL		Ratio	90% CI
	Nivestim	Neupogen		
5 µg/kg (n=23)	105223.09	95809.79	1.10	0.99 – 1.22*
10 µg/kg (n=24)	257841.09	221246.57	1.15	1.03 – 1.28*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Dose Group	Mean C_{max}, pg/mL		Ratio	90% CI
	Nivestim	Neupogen		
5 µg/kg (n=23)	17112.0	15187.5	1.13	0.98 – 1.30*
10 µg/kg (n=24)	37376.0	32628.7	1.14	1.00 – 1.29*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Pharmacokinetics in Special Populations

Paediatrics

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

Geriatrics

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

Renal or hepatic impairment

Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances. A trend towards higher systemic exposure to filgrastim is observed in patients with end-stage renal disease (ESRD) compared with healthy subjects and subjects with creatinine clearance of 30 - 60 mL/min.

5.3 Preclinical safety data

Carcinogenicity

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

Certain malignant cells have been shown to express G-CSF receptors. The possibility that filgrastim can act as a growth factor for any tumour type cannot be excluded.

Reproductive and developmental toxicity

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

Teratogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid

Nitrogen

Polysorbate 80

Sodium hydroxide

Sorbitol

Water for Injection

6.2 Incompatibilities

Nivestim should not be diluted with saline solutions; product may precipitate. If required, Nivestim may be diluted in 5% glucose.

6.3 Shelf life

30 months. This medicine should not be used after the expiry date shown on the pack.

After dilution: 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

Nivestim should be stored in a refrigerator at 2°C – 8°C.

Do not freeze. Keep the prefilled syringe in the outer carton in order to protect from light.

Brief accidental exposure to freezing temperatures for up to 24 hours does not affect the stability of Nivestim. The frozen prefilled syringes can be thawed and then refrigerated for future use. If exposure has been greater than 24 hours or frozen more than once then Nivestim 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.

6.5 Nature and contents of container

Nivestim Solution for Injection/Infusion is available as single use, preservative-free syringes containing either 120 µg filgrastim in 0.2 mL, 300 µg or 480 µg filgrastim in 0.5 mL.

Nivestim 120 µg/0.2 mL prefilled syringe	pack of 1, 5 or 10 prefilled syringes
Nivestim 300 µg/0.5 mL prefilled syringe	pack of 1, 5 or 10 prefilled syringes
Nivestim 480 µg/0.5 mL prefilled syringe	pack of 1, 5 or 10 prefilled syringes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Avoid vigorous shaking.

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

Nivestim prefilled syringes are for single use in one patient only. Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for dilution

If required, Nivestim may be diluted in 5% glucose. Dilution to a final concentration less than 5 µg/ mL is not recommended at any time.

For patients treated with Nivestim diluted to concentrations below 15 µg/mL, human serum albumin (HSA) should be added to a final concentration of 2 mg/mL to protect filgrastim from adsorption to plastic materials.

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

Diluted Nivestim solutions should not be prepared more than 24 hours before administration and should also be stored refrigerated at 2 – 8°C. Prior to injection, Nivestim may be allowed to reach room temperature.

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

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

24 May 2012

10. DATE OF REVISION OF THE TEXT

06 December 2023

Summary table of changes

Section changed	Summary of new information
4.4	To remove statement regarding "transient cytogenetic abnormalities" per clinical study data.
4.8	Update weblink for reporting suspected adverse reactions.
8	Update website address for consistent presentation.