AUSTRALIAN PRODUCT INFORMATION – NIVESTIM® (FILGRASTIM)

1. NAME OF THE MEDICINE

Filgrastim (rbe).

A Recombinant Human Granulocyte Colony Stimulating Factor (r-metHuG-CSF) derived from *E. coli*.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.2 mL pre-filled syringe contains 120 micrograms filgrastim.

Each 0.5 mL pre-filled syringe contains 300 micrograms or 480 micrograms filgrastim.

Nivestim is a 175 amino acid protein manufactured by recombinant DNA technology. Nivestim is produced by *Escherichia coli* bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It has a molecular weight of 18,800 daltons. Nivestim is unglycosylated and contains an N-terminal methionine necessary for expression in *E. coli*.

The specific activity of filgrastim by *in vitro* proliferative cell assay is 1 x 10^8 IU/mg when assayed against the WHO international standard for granulocyte colony stimulating factor, 88/502. The clinical significance of this *in vitro* potency assignment is unknown.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Nivestim is a sterile, clear, colourless, preservative-free liquid for parenteral administration, formulated in a 10 mM sodium acetate buffer at pH 4.0. The product is available in single use pre-filled syringes. The single use pre-filled syringes contain either 120 µg filgrastim at a fill volume of 0.2 mL or 300 µg or 480 µg filgrastim at a fill volume of 0.5 mL.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nivestim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs in doses not usually requiring bone marrow transplantation.

Nivestim is indicated for reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia (AML).

Nivestim is indicated for the mobilisation of autologous peripheral blood progenitor cells (PBPCs) alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil

and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with non-myeloid malignancies.

Nivestim is indicated for the mobilisation of PBPCs, in normal volunteers, for use in allogeneic peripheral blood progenitor cell (PBPC) transplantation.

In patients receiving myeloablative chemotherapy, Nivestim is indicated for reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation.

Nivestim is indicated for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia (SCN).

Nivestim is indicated in patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.

4.2 Dose and method of administration

Cancer patients receiving standard-dose cytotoxic chemotherapy or induction/consolidation chemotherapy for acute myeloid leukaemia

In adults and children receiving induction/consolidation chemotherapy for AML, the recommended starting dose is 5 µg/kg/day administered as a single daily subcutaneous (SC) injection.

In patients with non-myeloid malignancies receiving standard-dose cytotoxic chemotherapy, the recommended starting dose of Nivestim is 5 µg/kg/day administered as a single daily SC injection or short intravenous (IV) infusion (over 15 to 30 minutes). In phase 3 trials efficacy was observed at doses of 4 to 8 µg/kg/day.

Nivestim should not be administered in the period 24 hours before to 24 hours after the administration of chemotherapy (see Section 4.4 Special warnings and precautions for use).

The duration of Nivestim therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. In patients with non-myeloid malignancies receiving standard-dose cytotoxic chemotherapy, Nivestim should be administered daily for up to 2 weeks, until the absolute neutrophil count (ANC) has reached 10 x 10^9/L following the expected chemotherapy-induced neutrophil nadir. In patients with AML receiving induction or consolidation chemotherapy, Nivestim should be administered daily until the ANC has reached > 1.0 x 10^9/L for 3 consecutive days or > 10 x 10^9/L for 1 day following the expected chemotherapy-induced neutrophil nadir.

Patients with non-myeloid malignancies receiving high-dose cytotoxic chemotherapy with autologous or allogeneic bone marrow or peripheral blood progenitor cell transplantation

The recommended starting dose of Nivestim is 10 µg/kg/day given by continuous SC infusion or by IV infusion over 4 to 24 hours. Nivestim should be diluted in 25 to 50 mL of 5% glucose solution. The first dose of Nivestim should be administered not less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow or PBPC infusion.

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

Neutrophil Count	**Nivestim Dose Adjustment**
When ANC > 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 consecutive days	Discontinue Nivestim
If ANC decreases to < 1.0 x 10^9/L	Resume at 5 µg/kg/day

* If the ANC decreases to < 1.0 x 10^9/L at any time during the 5 µg/kg/day administration, Nivestim should be increased to 10 µg/kg/day and the above steps should then be followed.

Patients with myeloid malignancies receiving high-dose cytotoxic chemotherapy with autologous or allogeneic bone marrow or peripheral blood progenitor cell transplantation

Following transplant, the recommended dose of Nivestim to be given to the recipient is 5 µg/kg/day until neutrophil recovery (up to 28 days). When given post-transplantation, the first dose of Nivestim should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after infusion of bone marrow or PBPCs.

Autologous peripheral blood progenitor cell collection and therapy

The recommended dose of Nivestim for PBPC mobilisation when used alone is 10 µg/kg/day given as a single daily SC injection or a continuous 24-hour infusion.

Nivestim therapy should be given for at least 4 days before the first leukapheresis procedure and should be continued through to the day of the last leukapheresis procedure. Collections should be commenced on day 5 and continued on consecutive days until the desired yield of haemopoietic progenitor cells is obtained. For PBPCs mobilised with Nivestim alone, a schedule of leukapheresis collections on days 5, 6 and 7 of a 7-day treatment regimen has been found to be effective. In some patients with extensive prior chemotherapy, additional daily doses of Nivestim may be required to support additional leukaphereses to reach the desired target yield of cells (see Section 4.4 Special warnings and precautions for use, Peripheral blood progenitor cell collection and therapy, Prior exposure to cytotoxic agents).

The recommended dose of Nivestim for PBPC mobilisation after myelosuppressive chemotherapy is 5 µg/kg/day given daily by SC injection from 24 hours after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be commenced during the period when the ANC rises from < 0.5 x 10^9/L to > 5.0 x 10^9/L. Leukapheresis collection should be repeated on consecutive days until an adequate number of progenitor cells is obtained (see Section 4.4 Special warnings and precautions for use, Peripheral blood progenitor cell collection and therapy, Prior exposure to cytotoxic agents).

In all clinical trials of filgrastim for the mobilisation of PBPCs, filgrastim was administered following infusion of the collected cells. In the randomised phase 3 study, patients received filgrastim 5 µg/kg/day post-transplantation until a sustainable ANC (> 0.5 x 10^9/L) was reached (see Section 5.1 Pharmacodynamic properties, Clinical trials, Peripheral blood progenitor cell collection and therapy). When given post-transplantation, the first dose of Nivestim should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after infusion of PBPCs.

Allogeneic peripheral blood progenitor cell collection from normal donors

For PBPC mobilisation in normal donors, Nivestim should be administered at 10 µg/kg/day subcutaneously for 4 to 5 consecutive days. Leukapheresis should be started on day 5 and daily collections continued on day 6 in order to collect a target yield of 4 x 10^6 $CD34^+$ cells/kg recipient bodyweight.

Patients with severe chronic neutropenia

Diagnosis of SCN

Care should be taken to confirm the diagnosis of SCN, which may be difficult to distinguish from myelodysplastic syndrome (MDS), before initiating Nivestim therapy.

It is essential that serial FBCs with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of Nivestim therapy.

Starting dose

Congenital Neutropenia: The recommended daily starting dose is 12 µg/kg subcutaneously every day (single or divided doses).

Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 µg/kg subcutaneously every day (single or divided doses).

Nivestim may be administered subcutaneously as a single daily injection to increase and sustain the average neutrophil count above 1.5 x 10^9/L. Chronic daily administration is required to maintain an adequate neutrophil count.

Dose adjustment

After 1 to 2 weeks of therapy, the initial dose may be doubled or halved. Subsequently, the dose may be individually adjusted not more than every 1 to 2 weeks to maintain the average neutrophil count between 1.5 and 10 x 10^9/L. The dose should be reduced if the ANC is persistently above 10 x 10^9/L for 1 to 2 weeks.

In clinical trials, 97% of patients who responded to treatment with filgrastim were treated at doses ≤ 24 µg/kg/day. In the SCN post-marketing surveillance study, the reported median daily doses of filgrastim were: 6.0 µg/kg (congenital neutropenia), 2.1 µg/kg (cyclic neutropenia) and 1.2 µg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of filgrastim ≥ 100 µg/kg/day.

Patients with HIV infection

For reversal of neutropenia

The recommended starting dose of Nivestim is 1 µg/kg/day administered daily by SC injection with titration up to a maximum of 5 µg/kg/day until a normal neutrophil count is reached and can be maintained (ANC ≥ 2.0 x 10^9/L). In clinical studies, 96% of patients responded to filgrastim at these doses, achieving reversal of neutropenia in a median of 2 days.

In a small number of patients (2%), doses of up to 10 µg/kg/day were required to achieve reversal of neutropenia.

For maintaining neutrophil counts

When reversal of neutropenia has been achieved, the minimal effective dose of Nivestim to maintain a normal neutrophil count should be established. Initial dose adjustment to 3 times weekly 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 $\geq 2.0 \times 10^9$/L. In clinical studies, dosing with 300 µg/day on 1 to 7 days per week was required to maintain the ANC $\geq 2.0 \times 10^9$/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC $\geq 2.0 \times 10^9$/L. Nivestim dosing should be reduced and then stopped if myelosuppressive medication is discontinued and there is no recurrence of neutropenia.

Dilution

If required, Nivestim may be diluted in 5% glucose solution. Nivestim diluted to concentrations below 15 µg/mL should be protected from adsorption to plastic materials by addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% glucose solution or 5% glucose plus Albumin (Human) solution, Nivestim is compatible with glass and a variety of plastics including PVC, polyolefin and polypropylene.

Dilution to a final concentration of less than 5 µg/mL filgrastim is not recommended at any time. Do not dilute with saline at any time; product may precipitate. Infusion should be completed within 24 hours of the sterile dilution and transfer. Diluted Nivestim should not be prepared more than 24 hours before administration and should be stored in the refrigerator at 2° to 8°C. To reduce microbiological hazard, the solution should be administered as soon as practicable after dilution.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If particulates or discolouration are observed, the container should not be used.

4.3 Contraindications

Nivestim is contraindicated in patients with known hypersensitivity to *E. coli*-derived products, filgrastim, or any other component of the product.

4.4 Special warnings and precautions for use

General warnings and precautions across all indications

Splenomegaly and splenic rupture

Splenic rupture has been reported following administration of filgrastim; some of these cases were fatal. Left upper abdominal pain and/or shoulder tip pain accompanied by rapid increase in spleen size should be carefully monitored (e.g., clinical examination, ultrasound) due to the uncommon (≥ 1/1,000 and < 1/100) but serious risk of splenic rupture. Dose reductions of filgrastim have been noted to slow or stop the progression of splenic enlargement in patients with severe chronic neutropenia.

Patients with sickle cell disease

Clinicians should exercise caution and monitor patients accordingly when administering Nivestim to patients with sickle cell trait or sickle cell disease because of the reported association of filgrastim with sickle cell crisis (in some cases fatal).

Use of Nivestim in patients with sickle cell trait or sickle cell disease should be considered only after careful evaluation of the potential risks and benefits.

Thrombocytopenia

Thrombocytopenia has been reported commonly (≥ 1/100 and < 1/10) 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).

Pulmonary Adverse Effects

Pulmonary adverse effects, in particular interstitial lung disease, have been reported after G-CSF administration. There have been occasional reports of the occurrence of acute respiratory distress syndrome (ARDS) in patients receiving filgrastim. The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of lung infiltration and deterioration in pulmonary function may be preliminary signs leading to respiratory failure or ARDS. Nivestim should be immediately discontinued and appropriate treatment given.

Patients with a recent history of lung infiltrates or pneumonia may be at higher risk.

Pulmonary haemorrhage and haemoptysis

Pulmonary haemorrhage and haemoptysis requiring hospitalisation have been reported in filgrastim-treated healthy donors undergoing PBPC collection mobilisation. Haemoptysis resolved with discontinuation of filgrastim.

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim. 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 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.

Myelodysplastic syndrome or leukaemia

The safety and efficacy of filgrastim administration in patients with MDS or chronic myeloid leukaemia receiving myelosuppressive chemotherapy without stem cell support have not been established.

Randomised studies of filgrastim in patients undergoing chemotherapy for AML demonstrate no stimulation of disease as measured by remission rate, relapse and survival.

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.

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.

Capillary leak syndrome

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after granulocyte colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, 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 (see Section 4.8 Adverse effects (undesirable effects)).

Osteoporosis

Monitoring of bone density according to local clinical practice may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with filgrastim.

Cancer patients receiving myelosuppressive chemotherapy

Concurrent use with chemotherapy and radiotherapy

The safety and efficacy of filgrastim given concurrently with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, the use of filgrastim is not recommended in the period 24 hours before to 24 hours after the administration of chemotherapy (see Section 4.2 Dose and method of administration).

No controlled study has been done to examine the combination of chemoradiotherapy and filgrastim on platelet count in a suitable oncology setting. Therefore, until more definitive data are available, simultaneous use of filgrastim with chemoradiation should be undertaken with caution.

Leukocytosis

White blood cell (WBC) counts of 100 x 10^9/L or greater were observed in approximately 2% of patients receiving filgrastim at doses above 5 µg/kg/day. There were no reports of adverse

events associated with this degree of leukocytosis. In order to avoid the potential complications of excessive leukocytosis, a full blood count (FBC) is recommended twice per week during filgrastim therapy. (see Section 4.4 Special warnings and precautions for use, Laboratory monitoring).

Premature discontinuation of Nivestim therapy

A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, Nivestim therapy should be continued until the post nadir ANC reaches 10 x 10^9/L. Therefore, the premature discontinuation of filgrastim therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see Section 4.2 Dose and method of administration).

Risks associated with increased doses of chemotherapy

In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see Section 4.8 Adverse effects (undesirable effects)). Because of the potential of receiving higher doses of chemotherapy (i.e. full doses on the prescribed schedule for a longer period), the patient may be at greater risk of thrombocytopenia which should be monitored carefully. Anaemia and non-haematological consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used) also may occur. Regular monitoring of the haematocrit and platelet count is recommended. Furthermore, care should be exercised in the administration of filgrastim in conjunction with drugs known to lower the platelet count and in the presence of moderate or severe organ impairment. Thrombocytopenia may be more severe than normal in later courses of chemotherapy.

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

Peripheral blood progenitor cell collection and therapy

Mobilisation

There are no prospectively randomised comparisons of the 2 recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between both different patient groups and results of laboratory assays of $CD34^+$ cells means that direct comparison between different studies is difficult and an optimum method cannot yet be recommended. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

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. Recommendations for minimum acceptable progenitor cell yield based on studies using methods other than that of the reporting laboratory need to be interpreted with caution.

Statistical analysis of the relationship between the number of $CD34^+$ cells infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship, with the probability of more rapid platelet recovery increasing as the $CD34^+$ cell yield increases.

Currently, the minimum acceptable yield of $CD34^+$ cells is not well defined. The recommendation of a minimum yield of $\geq 2 \times 10^6$ $CD34^+$ cells/kg is based on published experience resulting in adequate haematologic reconstitution.

Prior exposure to cytotoxic agents

Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPCs to achieve the recommended minimum yield ($\geq 2 \times 10^6$ $CD34^+$ cells/kg) or acceleration of platelet recovery, to the same degree. When PBPC transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitor cells mobilised in such patients before the administration of high-dose chemotherapy.

In one phase 2 study in heavily pretreated patients with acute lymphoblastic leukaemia, non-Hodgkin's lymphoma or Hodgkin's disease, no increased yield of progenitor cells was demonstrated by increasing the dose of filgrastim beyond that recommended.

If yields are inadequate, as measured by the criterion above, alternative forms of treatment not requiring progenitor cell support should be considered.

Some cytotoxic agents exhibit particular toxicities to the haemopoietic progenitor pool and may adversely affect progenitor cell mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor cell mobilisation, may reduce progenitor cell yield. Nevertheless, the administration of melphalan, carboplatin or BCNU together with filgrastim, has been shown to be effective for progenitor cell mobilisation.

Leukocytosis

During the period of administration of filgrastim for PBPC mobilisation in cancer patients, discontinuation of filgrastim is appropriate if the leukocyte count rises to $> 100 \times 10^9$/L (see Section 4.4 Special warnings and precautions for use, Cancer patients receiving myelosuppressive chemotherapy, Leukocytosis).

Tumour contamination of bone marrow and leukapheresis products

Some studies of patient bone marrow and leukapheresis products have demonstrated the presence of malignant cells. While the possibility exists for tumour cells to be released from the marrow during mobilisation of PBPCs and subsequently collected in the leukapheresis product, in most of the studies, leukapheresis products appear to be less contaminated than bone marrow from the same patient. The effect of reinfusion of tumour cells has not been well studied and the limited data available are inconclusive.

Normal donors undergoing peripheral blood progenitor cell mobilisation

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

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

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

Transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, 2 cases of platelets < 50 x 10^9/L were reported and attributed to the leukapheresis procedure.

If more than 1 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.

Nivestim administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 100 x 10^9/L.

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

Insertion of a central venous catheter should be avoided where possible, and therefore consideration should be given to the adequacy of venous access when selecting donors.

Long-term safety follow-up of donors is ongoing. For up to 4 years, there have been no reports of abnormal haematopoiesis in normal donors. Nevertheless, a risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors to ensure monitoring of long-term safety.

There have been uncommon (≥ 1/1,000 and < 1/100) cases of splenic rupture reported in healthy donors following administration of G-CSFs. In donors experiencing left upper abdominal pain and/or shoulder tip pain and rapid increase in spleen size, the risk of splenic rupture should be considered and carefully monitored.

In normal donors, pulmonary adverse events (haemoptysis, lung infiltration) have been reported.

Recipients of allogeneic peripheral blood progenitor stem cells 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.

Patients with severe chronic neutropenia

Diagnosis of SCN

Care should be taken to confirm the diagnosis of SCN, which may be difficult to distinguish from MDS, before initiating filgrastim therapy. The safety and efficacy of filgrastim in the treatment of neutropenia or pancytopenia due to other haemopoietic disorders (e.g., myelodysplastic disorders or myeloid leukaemia) have not been established.

It is, therefore, essential that serial FBCs with differential and platelet counts and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of filgrastim

therapy. The use of filgrastim prior to diagnostic confirmation of SCN may mask neutropenia as a diagnostic sign of a disease process other than SCN and prevent adequate evaluation and appropriate treatment of the underlying condition causing the neutropenia.

Myelodysplastic syndrome and acute myeloid leukaemia

Cytogenetic abnormalities, transformation to MDS and AML have been observed in patients treated with filgrastim for SCN. MDS and AML have been reported to occur in the natural history of SCN without cytokine therapy. Based on available data including a post-marketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia (see Section 4.8 Adverse effects (undesirable effects)). Abnormal cytogenetics have been associated with the development of myeloid leukaemia. The effect of filgrastim on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or MDS, the risks and benefits of continuing filgrastim should be carefully considered.

Patients with HIV infection

Risks 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 medications with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia.

Regular monitoring of blood counts is recommended (see Section 4.4 Special warnings and precautions for use, Laboratory monitoring, Patients with HIV infection).

Infections and malignancies causing myelosuppression

Neutropenia may also 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 infection or malignancy, consideration should be given to appropriate therapy for treatment of the underlying condition. 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 potential for immunogenicity. Rates of antibody generation against filgrastim are generally low. Binding antibodies do develop but have not been associated with neutralising activity or adverse clinical consequences.

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

Cancer patients receiving myelosuppressive chemotherapy

An FBC, haematocrit and platelet count should be obtained prior to chemotherapy and at regular intervals (twice per week) during filgrastim therapy. Following cytotoxic

chemotherapy, the neutrophil nadir occurred earlier during cycles when filgrastim was administered and WBC differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced and was followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of WBC counts, particularly at the time of the recovery from the post chemotherapy nadir is recommended in order to avoid excessive leukocytosis (see Section 4.2 Dose and method of administration).

Peripheral blood progenitor cell collection and therapy

After 4 days of filgrastim treatment for PBPC mobilisation, neutrophil counts should be monitored. Frequent complete blood counts and platelet counts are recommended following infusion of PBPCs, at least 3 times per week until haemopoietic recovery.

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 haemopoietic progenitor cells can be appropriately performed and interpreted (see Section 4.4 Special warnings and precautions for use, Peripheral blood progenitor cell collection and therapy).

Patients with severe chronic neutropenia

During the initial 4 weeks of filgrastim therapy and for 2 weeks following any dose adjustment, an FBC with differential count should be performed twice weekly. Once a patient is clinically stable, an FBC with differential count and platelet determination should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular FBCs (i.e. as clinically indicated but at least quarterly) is recommended. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment (see Sections 4.4 Special warnings and precautions for use, Patients with severe chronic neutropenia and 4.8 Adverse effects (undesirable effects)).

In clinical trials, the following laboratory results were observed:

- Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of filgrastim therapy.

- Platelet counts were generally at the upper limits of normal prior to filgrastim therapy. With filgrastim therapy, platelet counts decreased but generally remained within normal limits (see Section 4.8 Adverse effects (undesirable effects)).

- Early myeloid forms were noted in peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients.

- Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with filgrastim therapy.

Patients with HIV infection

ANC should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly with a considerable increase in neutrophil count after initial doses 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 per week for the first 2 weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 300 µg of filgrastim, there will 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 for ANC measurement are obtained immediately prior to any scheduled dosing with filgrastim.

All patients

Nivestim contains sorbitol (E420). Patients with rare 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 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.

Use in the elderly

No special studies have been performed in the elderly and therefore no specific dosage recommendations can be made for Nivestim.

Paediatric use

Long-term follow-up data are available from a post-marketing surveillance study in SCN patients including 32 infants, 200 children and 68 adolescents. The data suggest that height and weight are not adversely affected in paediatric patients who received up to 5 years of filgrastim treatment. Limited data from patients who were followed in a phase 3 study to assess the safety and efficacy of filgrastim in SCN for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Paediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown (see Sections 4.4 Special warnings and precautions for use, Patients with severe chronic neutropenia and 4.8 Adverse effects (undesirable effects)).

Although use in children with AML is not excluded, published experience is limited and safety has not been clearly established.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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.

Cancer patients receiving myelosuppressive chemotherapy

No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see Section 4.4 Special warnings and precautions for use, Cancer patients receiving myelosuppressive chemotherapy, Concurrent use with chemotherapy and radiotherapy).

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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy

Pregnancy category B3

There are no sponsored studies of the use of filgrastim in pregnant women. However, there are cases in the literature where the transplacental passage of filgrastim has been demonstrated. Filgrastim should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

Reproductive studies in pregnant rats have shown that filgrastim was not associated with lethal, teratogenic or behavioural effects on fetuses when administered by daily IV injection during the period of organogenesis at dose levels up to 575 µg/kg/day. The administration of filgrastim to pregnant rabbits during the period of organogenesis at doses of 20 µg/kg/day IV or greater was associated with an increased incidence of embryonic loss, urogenital bleeding and decreased food consumption. External abnormalities were not observed in the fetuses of treated does, but there was a significant increase in the incidence of fusion of sternebrae at an 80 µg/kg/day dose. The administration of filgrastim to pregnant rabbits at a dose of 5 µg/kg/day IV was not associated with observable adverse effects to the doe or fetus.

Use in lactation

It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised in the use of filgrastim in nursing women.

4.7 Effects on ability to drive and use machines

Filgrastim may have a minor influence on the ability to drive and use machines. Dizziness may occur following the administration of filgrastim (see Section 4.8 Adverse effects (undesirable effects)).

4.8 Adverse effects (undesirable effects)

Summary of the safety profile

The most serious adverse reactions that may occur during filgrastim treatment include: anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, severe splenomegaly/splenic rupture, transformation to myelodysplastic syndrome or leukaemia in SCN patients, GvHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant and sickle cell crisis in patients with sickle cell disease (see Section 4.4 Special warnings and precautions for use).

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting and nausea.

Cancer patients receiving myelosuppressive chemotherapy

In clinical trials involving over 200 patients receiving filgrastim following cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase 2/3 trials, medullary bone pain was the only consistently observed adverse reaction attributed to filgrastim therapy, reported in 24% of patients. This bone pain was generally reported to be of mild-to-moderate severity and could be controlled in most patients with non-narcotic analgesics. Infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20 to 100 µg/kg/day) administered intravenously and less frequently in patients treated with lower SC doses of filgrastim (3 to 10 µg/kg/day).

In the randomised, double-blind, placebo-controlled trial of filgrastim therapy following combination chemotherapy in patients with small cell lung cancer, the following adverse events were reported to be possibly, probably or definitely related to the double-blind study medication (placebo or filgrastim at 4 to 8 µg/kg/day):

Clinical Adverse Events by Body System Reported to be Related to Double-blind Study Medication		
	% of Patients with Reported Events	
	Placebo	Filgrastim
Body system	N = 68	N = 69
Musculoskeletal	1.5	12.0
Integumentary	6.0	6.0
Body as a whole	5.0	4.3
Neurologic/psychiatric	3.0	4.3

Clinical Adverse Events by Body System Reported to be Related to Double-blind Study Medication		
	% of Patients with Reported Events	
	Placebo	Filgrastim
Respiratory	1.5	3.0
Vascular disorders	1.5	3.0
Local reaction	1.5	1.4
Thrombocytopenia/coagulation	2.9	NR
Autonomic nervous system	NR	1.4
Special senses	NR	1.4

NR = not reported

In this study, there were no serious, life-threatening or fatal adverse reactions attributed to filgrastim therapy. Specifically, there were no reports of flu-like symptoms, pleuritis, pericarditis or other major systemic reactions to filgrastim.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase and alkaline phosphatase occurred in 26% to 56% of patients receiving filgrastim following cytotoxic chemotherapy. These elevations were not reported to be associated with clinical adverse events.

The occurrence of stomatitis and diarrhoea in patients receiving allogeneic transplants is consistent with the use of myeloablative chemotherapy. In a study of 70 patients undergoing allogeneic bone marrow transplantation in which 33 patients were randomised to the placebo group and 37 to the filgrastim group, the incidence and severity of diarrhoea and stomatitis increased from the pre-to the post-transplant period in both the placebo and filgrastim treated patients. Prior to transplantation, 12 patients randomised to the placebo group and 6 patients randomised to filgrastim reported moderate-to-severe diarrhoea. Following transplantation, the incidence of moderate-to-severe diarrhoea increased to 23 and 14 patients respectively. No patients in either group experienced moderate or severe stomatitis prior to transplantation, while after transplantation, 19 patients in the placebo group and 8 patients in the filgrastim group reported moderate-to-severe stomatitis.

In a randomised, double-blind, placebo-controlled phase 3 study of patients with AML, there were 3 patients reported to have developed ARDS during the study (2 filgrastim, 1 placebo). This is a rare but expected event in this patient population and all 3 patients had recognised predisposing factors. As a causal relationship between the development of ARDS and filgrastim treatment has not been established and as multiple risk factors are often present, any decision to discontinue filgrastim in this setting should be based on the overall assessment of contributing factors.

Extremely rare cases of capillary leak syndrome have been reported.

Rare cases (≥ 1/10,000 to < 1/1,000) of Sweet's syndrome (acute febrile neutrophilic dermatosis) have been reported.

Very rare (estimated 0.03 cases per 100,000 exposures [0.00003%]) events of chondrocalcinosis pyrophosphate have been reported in patients with cancer treated with filgrastim.

Chronic administration

With chronic administration, clinical splenomegaly has been reported in 30% of patients. Less frequently observed adverse events included exacerbation of some pre-existing skin disorders (e.g., psoriasis), cutaneous vasculitis (leukocytoclastic), alopecia, haematuria/proteinuria, thrombocytopenia (platelets < 50 x 10^9/L) and osteoporosis. Patients receiving chronic treatment with filgrastim should be monitored periodically for the appearance of these conditions.

No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see Section 4.4 Special warnings and precautions for use, Cancer patients receiving myelosuppressive chemotherapy, Concurrent use with chemotherapy and radiotherapy). Since commercial introduction of filgrastim there have been rare reports (< 1 in 100,000 administrations) of symptoms suggestive of allergic-type reactions such as anaphylaxis, dyspnoea, hypotension, skin rash and urticaria, but in which an immune component has not been demonstrated. Approximately half occurred following the initial dose; reactions occurred more frequently with IV administration. Symptoms recurred in some patients rechallenged. There have been rare reports (< 1 in 500,000 administrations) of cutaneous vasculitis. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

In chronically treated patients, including some who have received filgrastim daily for almost 2 years, there has been no evidence of the development of antibodies to filgrastim or a blunted or diminished response over time.

Peripheral blood progenitor cell collection and therapy

Filgrastim-mobilised autologous PBPC collection

In clinical trials, 126 patients have received filgrastim for mobilisation of PBPCs. During the mobilisation period, adverse events related to filgrastim consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (38%). Headache was reported related to filgrastim in 7% of patients. Mild-to-moderate transient increases in alkaline phosphatase levels were reported related to filgrastim in 21% of the patients who had serum chemistries evaluated during the mobilisation phase.

All patients had increases in neutrophil counts consistent with the biological effects of filgrastim. Two patients had a WBC count greater than 100 x 10^9/L with WBC count increases during the mobilisation period ranging from 16.7 to 138 x 10^9/L above baseline. Eighty-eight percent of patients had an increase in WBC count between 10 and 70 x 10^9/L above baseline. No clinical sequelae were associated with any grade of leukocytosis.

Sixty-five percent of patients had downward shifts in haemoglobin, which were generally mild-to-moderate (59%) and 97% of patients had decreases in platelet counts related to the leukapheresis procedure. Only 2 patients had platelet counts less than 50 x 10^9/L.

Allogeneic peripheral blood progenitor cell mobilisation in normal donors

The most commonly reported adverse event was mild-to-moderate transient musculoskeletal pain. 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.

Transient, minor increases in alkaline phosphatase, LDH, AST and uric acid have been reported in normal donors receiving filgrastim; these were without clinical sequelae.

Exacerbation of arthritic symptoms has been observed very rarely.

Symptoms suggestive of severe allergic reactions have been reported very rarely.

Headaches, believed to be caused by filgrastim, have been reported in PBPC donor studies.

There have been uncommon (≥ 1/1,000 and < 1/100) cases of splenic rupture reported in normal donors receiving G-CSFs (see Section 4.4 Special warnings and precautions for use).

Extremely rare cases of capillary leak syndrome have been reported.

In normal donors, pulmonary adverse events (haemoptysis, lung infiltration) have been reported.

PBPC transplantation supported by filgrastim

During the period of filgrastim administration post infusion of autologous PBPCs, filgrastim was administered to 110 patients as supportive therapy and adverse events were consistent with those expected after high-dose chemotherapy. Mild-to-moderate musculoskeletal pain was the most frequently reported adverse event related to filgrastim, reported in 15% of patients. In patients receiving allogeneic PBPCs, a similar incidence of musculoskeletal pain was reported.

Patients with severe chronic neutropenia

The safety and efficacy of chronic daily administration of filgrastim in patients with SCN have been established in phase 1/2 clinical trials of 74 patients treated for up to 3 years and in a phase 3 trial of 123 patients treated for up to 2 years.

Mild-to-moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was readily controlled with mild analgesics. General musculoskeletal pain was also noted in higher frequency in patients treated with filgrastim. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently and thrombocytopenia (< 50 x 10^9/L) was noted in 12% of patients with palpable spleens. Less than 3% of all patients underwent splenectomy and most of these had a prestudy history of splenomegaly. Less than 6% of patients had thrombocytopenia (< 50 x 10^9/L) during filgrastim therapy, most of whom had a prestudy history. In most cases, thrombocytopenia was managed by filgrastim dose reduction or interruption. There were no associated serious haemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with filgrastim but was associated with thrombocytopenia in 2% of patients. Anaemia was reported in approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness or concomitant medications.

Cytogenetic abnormalities, transformation to MDS and AML have been observed in patients treated with filgrastim for SCN (see Section 4.4 Special warnings and precautions for use, Paediatric use). Based on analysis of data from a post-marketing surveillance study of 531 SCN patients with an average follow-up of 4.0 years, the risk of developing these abnormalities (cytogenetic abnormalities, MDS and AML) appears to be confined to the subset of patients with congenital neutropenia. A life-table analysis of these data revealed that the cumulative risk of developing leukaemia or MDS by the end of the 8th year of filgrastim treatment in a patient with congenital neutropenia was 16.5% which is an annual rate of approximately 2%.

Cytogenetic abnormalities, including monosomy 7, have been reported in patients treated with filgrastim who had previously documented normal cytogenetic evaluations. It is unknown whether the development of cytogenetic abnormalities, MDS or AML is related to chronic daily filgrastim administration or to the natural history of SCN. It is also unknown if the rate of conversion in patients who have not received filgrastim is different from that of patients who have received filgrastim. Routine monitoring through regular FBCs is recommended for all SCN patients. Additionally, annual bone marrow and cytogenetic evaluations are recommended in all patients with congenital neutropenia (see Section 4.4 Special warnings and precautions for use, Laboratory monitoring).

Other adverse events infrequently observed and possibly related to filgrastim therapy were: injection site reaction, headache, hepatomegaly, arthralgia, osteoporosis, rash, alopecia, cutaneous vasculitis and haematuria/proteinuria. Patients receiving chronic treatment with filgrastim should be monitored periodically for the appearance of these conditions.

In post-marketing experience, common ($\geq$ 1/100 and < 1/10) cases of decreased bone density and osteoporosis have been reported in paediatric patients with SCN receiving chronic treatment with filgrastim.

Patients with HIV infection

In 3 clinical studies involving a total of 244 HIV-positive patients, the only adverse events that were consistently considered related to filgrastim administration were musculoskeletal pain, predominantly mild-to-moderate bone pain and myalgia. In the largest of the 3 studies involving 200 patients, the event rate was 12%. This is consistent with the 14% incidence of musculoskeletal pain reported in clinical trials in other indications where doses of 0.35 to 11.5 µg/kg/day were used. The incidence of severe musculoskeletal pain (3%) was identical to that reported in clinical trials in other indications.

In a small study of 24 patients, there were 7 reports of treatment-related splenomegaly, but in a larger study of 200 patients, there were no such reports. In the former study, no baseline measurements of spleen size were made for comparison with on-study measurements. In all cases, splenomegaly 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.

An analysis was performed on viral load data, as measured by HIV-1 RNA polymerase chain reaction (PCR), from a controlled randomised study of filgrastim for the prevention of grade 4 neutropenia. No clinically or statistically significant differences were seen between filgrastim treated groups and untreated groups for changes in viral load over a 24-week period. However, since the study was not powered to show equivalence between the groups, the possibility that filgrastim affects HIV-1 replication cannot be excluded. There was also no detrimental effect on immunological markers, which is important in a population of patients in whom a decline in $CD4^+$ T-lymphocyte count is expected. There were no safety concerns with long-term administration of filgrastim in this setting.

Adverse reactions relevant to all indications

In combined clinical trial data, adverse reactions are listed below. Adverse reactions observed in the combined clinical trial data which are present in the adverse effects sections by indication above 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, asthenia, 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 haematopoiesis, exacerbation of rheumatoid arthritis.

Comparability of Nivestim with Neupogen®

During clinical studies 183 cancer patients and 96 healthy volunteers were exposed to Nivestim. The safety profile of Nivestim observed in these clinical studies was consistent with that observed for Neupogen.

Post-marketing experience relevant to all indications

Cases of splenomegaly have been reported commonly (≥ 1/100 and < 1/10) in patients treated with filgrastim (see Section 4.4 Special warnings and precautions for use).

Cases of splenic rupture, sickle cell anaemia with crisis and glomerulonephritis have been reported uncommonly (≥ 1/1,000 and < 1/100) in patients treated with filgrastim (see Section 4.4 Special warnings and precautions for use).

Cases of pulmonary haemorrhage, lung infiltration and haemoptysis have been reported in patients receiving filgrastim (see Section 4.4 Special warnings and precautions for use). Interstitial lung disease, pulmonary oedema and hypoxia have also been reported.

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.

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

Description of selected adverse reactions

Hypersensitivity

Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post-marketing experience. Overall, reports were more common after IV administration.

In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

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 Special warnings and precautions for use).

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 of SCN patients.

Leukocytosis

Leukocytosis (WBC > 50 × 10^9/L) was observed in 41% of normal donors and transient thrombocytopenia (platelets < 100 × 10^9/L) following filgrastim and leukapheresis was observed in 35% of donors (see Section 4.4 Special warnings and precautions for use).

Sweets syndrome

Cases of Sweets syndrome (acute febrile neutrophilic dermatosis) have 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 (see Sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

The maximum tolerated dose of Nivestim has not been determined. Twenty seven patients have been treated at filgrastim doses of ≥ 69 µg/kg/day. Of those, 6 patients have been treated at 115 µg/kg/day with no toxic effects attributable to filgrastim. Efficacy has been demonstrated using much lower doses (doses of 4 to 8 µg/kg/day showed efficacy in the phase 3 study). Doses of Nivestim which increase the ANC beyond 10 x 10^9/L may not result in any additional clinical benefit.

In clinical trials of filgrastim in cancer patients receiving myelosuppressive chemotherapy, WBC counts > 100 x 10^9/L have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects.

It is recommended, to avoid the potential risks of excessive leukocytosis, that Nivestim therapy should be discontinued if the ANC surpasses 10 x 10^9/L after the chemotherapy-induced ANC nadir has occurred.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pre-treatment levels in 1 to 7 days.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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

Endogenous filgrastim (i.e. granulocyte colony stimulating factor) is a lineage-specific colony stimulating factor with selectivity for the neutrophil lineage. Filgrastim is not species specific and has been shown to primarily affect neutrophil progenitor proliferation, differentiation and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing and the increased expression of some functions associated with cell surface antigens).

The results of all preclinical studies indicate that the pharmacologic effects of filgrastim are consistent with its predominant role as a regulator of neutrophil production and function.

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 SC 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. IV and SC 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. SC administration of multiple (five) 5 μg/kg and 10 μg/kg doses provided similar ANC $AUC_{0\text{-tlast}}$ and $CD34^+$ values.

	Mean ANC $AUC_{0\text{-tlast}}$, 10^9.h/L			
Dose Group	Nivestim	Neupogen	Ratio	90% CI
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

	Mean $CD34^+$ count, cells/μL (range)			
Dose Group	Nivestim	Neupogen	Ratio	90% CI
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

Clinical trials

Cancer patients receiving myelosuppressive chemotherapy

In all clinical studies, administration of filgrastim resulted in a dose-dependent rise in neutrophil counts. Following termination of filgrastim therapy, circulating neutrophil counts declined by 50% within 1 to 2 days and to pretreatment levels within 1 to 7 days. Isolated neutrophils displayed normal phagocytic and chemotactic activity *in vitro*.

In a study of the effects of filgrastim in patients with carcinoma of the urothelium, repeated daily IV dosing with filgrastim resulted in a linear dose-dependent increase in circulating neutrophil counts over the dose range of 1 to 70 μg/kg/day. The effects of filgrastim therapy reversed within 24 hours of the termination of administration and neutrophil counts returned to baseline, in most cases, within 4 days.

In a phase 1 study of patients with a variety of malignancies, including lymphoma, multiple myeloma and adenocarcinoma of the lung, breast and colon, filgrastim induced a dose-dependent increase in neutrophil counts. This increase in neutrophil counts was observed whether filgrastim was administered intravenously (1 to 70 μg/kg twice daily), subcutaneously (1 to 3 μg/kg once daily) or by continuous SC infusion (3 to 11 μg/kg/day).

These results were consistent with a phase 1 study of patients with small cell lung cancer who were administered filgrastim prior to chemotherapy. All patients responded to filgrastim (1 to 45 μg/kg/day), given for 5 days, with a dose-dependent increase in median neutrophil count from a baseline of 9.5 x 10^9/L to a maximum response of 43 x 10^9/L.

In a randomised, double-blind, placebo-controlled phase 3 study of small cell lung cancer patients receiving combination chemotherapy (cyclophosphamide, doxorubicin and etoposide), treatment with filgrastim resulted in clinically and statistically significant reductions in both the incidence and duration of infection, as manifested by febrile neutropenia. The incidence, severity and duration of severe neutropenia (ANC < 0.5 x 10^9/L) following chemotherapy were all significantly reduced, as were the requirements for in-patient hospitalisation and antibiotic use (see Section 4.8 Adverse effects (undesirable effects)). With other myelosuppressive

regimens (e.g., M-VAC, melphalan), a dose-dependent increase in neutrophil counts was observed, as well as a decrease in the duration of severe neutropenia.

In a randomised, double-blind, placebo-controlled phase 3 study of patients with AML, the median duration of neutropenia (ANC < 0.5 x 10^9/L) during the first induction cycle was significantly reduced, from 19 days in the placebo group to 14 days in the filgrastim group. The duration of hospitalisation during induction therapy was also significantly reduced in the filgrastim group, from 29 days to 23 days, as were the duration of fever and incidence of IV antibiotic use. Filgrastim had a similar impact on the durations of neutropenia, hospitalisation, fever and IV antibiotic use in subsequent cycles of chemotherapy.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving filgrastim. The percentage of monocytes in the differential count was within the normal range. In all studies to date, absolute counts of both eosinophils and basophils were within the normal range following administration of filgrastim. Small non-dose-dependent increases in lymphocyte counts following filgrastim administration have been reported in normal subjects and cancer patients.

Peripheral blood progenitor cell collection and therapy

Use of filgrastim, either alone, or after chemotherapy, mobilises haemopoietic progenitor cells into the peripheral blood. These PBPCs may be harvested and infused after high-dose chemotherapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates the rate of neutrophil and platelet recovery reducing the risk of haemorrhagic complications and the need for platelet transfusions.

In a randomised phase 3 study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received autologous filgrastim-mobilised peripheral blood progenitor cell transplantation (PBPCT) followed by filgrastim 5 µg/kg/day and 31 patients received autologous bone marrow transplantation (ABMT) followed by filgrastim 5 µg/kg/day. Patients randomised to the filgrastim-mobilised PBPCT group compared to the ABMT group had significantly fewer median days of platelet transfusions (6 vs 10 days), a significantly shorter median time to a sustained platelet count > 20 x 10^9/L (16 vs 23 days), a significantly shorter median time to recovery of a sustained ANC ≥ 0.5 x 10^9/L (11 vs 14 days) and a significantly shorter duration of hospitalisation (17 vs 23 days).

In all clinical trials of filgrastim for the mobilisation of PBPCs, filgrastim (5 to 24 µg/kg/day) was administered until a sustainable ANC (≥ 0.5 x 10^9/L) was reached.

Overall, infusion of filgrastim-mobilised PBPCs, supported by filgrastim post-transplantation, provided rapid and sustained haematologic recovery. Long-term (approximately 100 days) follow-up haematology data from patients treated with autologous PBPCT alone or in combination with bone marrow was compared to historical data from patients treated with ABMT alone. This retrospective analysis indicated that engraftment is durable.

In a randomised trial comparing filgrastim-mobilised allogeneic PBPCT with allogeneic BMT in patients with acute leukaemia, chronic myelogenous leukaemia or myelodysplastic syndrome, filgrastim was given at 10 µg/kg/day to 163 healthy volunteers for 4 to 5 days followed by leukapheresis beginning on day 5. Another 166 healthy volunteers donated bone marrow. The number of $CD34^+$ cells in the leukapheresis product was generally sufficient to support a transplant, with over 80% of donors achieving the target yield of 4 x 10^6/kg recipient bodyweight. In the vast majority of donors (95%) sufficient PBPCs (2 x 10^6 $CD34^+$ cells/kg of

recipient) were obtained in ≤ 2 leukaphereses. The median number of $CD34^+$ cells in the leukapheresis product (5.8 x 10^6/kg) was higher than that of bone marrow product (2.7 x 10^6/kg); however, the product from both procedures was sufficient to allow each recipient to receive a transplant. Following transplant, all recipients received filgrastim at 5 µg/kg/day until neutrophil recovery (up to 28 days). Recipients of allogeneic PBPC had a shorter median time to platelet recovery of ≥ 20 x 10^9/L (15 vs 20 days) and shorter median time to ANC recovery of ≥ 0.5 x 10^9/L (12 vs 15 days). There was no difference in leukaemia free survival at a median follow-up of 12 months.

Patients with severe chronic neutropenia

In a randomised, controlled, open-label phase 3 trial of 123 patients with idiopathic, cyclic and congenital neutropenia, untreated patients had a median ANC of 0.21 x 10^9/L. filgrastim therapy was adjusted to maintain the median ANC between 1.5 and 10 x 10^9/L. A complete response was seen in 88% of patients (defined as a median ANC ≥ 1.5 x 10^9/L) over 5 months of filgrastim therapy. Overall, the response to filgrastim therapy for all patients was observed in 1 to 2 weeks.

The median ANC after 5 months of filgrastim therapy for all patients was 7.46 x 10^9/L (range 0.03 to 30.88 x 10^9/L). In general, patients with congenital neutropenia responded to filgrastim therapy with lower median ANC than patients with idiopathic or cyclic neutropenia.

Overall, daily treatment with filgrastim resulted in clinically and statistically significant reductions in the incidence and duration of fever, infections and oropharyngeal ulcers. As a result, there also were substantial decreases in requirements for antibiotic use and hospitalisation. Additionally, patients treated with filgrastim reported fewer episodes of diarrhoea, nausea, fatigue and sore throat.

Patients with HIV infection

In an open-label, non-comparative study involving 200 HIV-positive patients with neutropenia (ANC < 1.0 x 10^9/L), filgrastim reversed the neutropenia in 98% of patients (ANC ≥ 2.0 x 10^9/L) with a median time to reversal of 2 days (range 1 to 16) and a median dose of 1 µg/kg/day (range 0.5 to 10). Ninety-six percent of patients achieved reversal of neutropenia with a dose of ≤ 300 µg/day. Normal ANCs were then maintained with a median dose frequency of 3 times 300 µg vials/week (range 1 to 7). Ganciclovir, zidovudine, co-trimoxazole and pyrimethamine were the medications most frequently considered to be causing neutropenia and 83% of patients received 1 or more of these on-study. During the study, 84% of these patients were able to increase or maintain dosing of these 4 medications or add them to their therapy. The number of these 4 medications received per patient increased by more than 20% (from 0.98 to 1.18) during filgrastim therapy. The median duration of filgrastim treatment was 191 days (range 2 to 815). One hundred and fifty-three patients received long-term maintenance therapy (> 58 days) and the frequency of dosing was similar to that in the first 30 days of maintenance therapy (71% of patients were receiving 2 to 3 vials per week).

Overall, in patients with HIV infection filgrastim rapidly reverses neutropenia and is subsequently able to maintain normal neutrophil counts during chronic administration.

Comparability of Nivestim with Neupogen

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 < 0.5×10^9/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 > 3×10^9/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

In normal volunteers, serum filgrastim concentrations declined monoexponentially following a single IV infusion, exhibiting a half-life of approximately 3 hours. Clearance and volume of distribution averaged 0.6 mL/minute/kg and 163 mL/kg. Following a single SC injection, peak serum concentrations of filgrastim occurred at approximately 4 to 6 hours. The absorption phase can be fitted to either a zero-order or a first-order model whereas the elimination phase observed a monoexponential decline. No difference in half-lives were observed following IV and SC doses. The bioavailability was estimated to be approximately 50% following SC administration.

In cancer patients, clearance and volume of distribution of filgrastim were found to be lower than in normal volunteers, averaging approximately 0.12 to 0.34 mL/minute/kg and 56 to 127 mL/kg, respectively. However, the elimination half-life appeared to be similar when compared to normal volunteers, averaging 3 to 4 hours. Following a single SC injection of 3.45 μg/kg and 11.5 μg/kg, peak serum concentrations occurred at approximately 4 to 5 hours and averaged 4 ng/mL and 49 ng/mL. Continuous SC infusions of 23 μg/kg of filgrastim over 24 hours in cancer patients resulted in a steady-state concentration of approximately 50 (30 to 70) ng/mL. No evidence of drug accumulation was observed over 11 to 20 days of continuous infusion. When a single IV dose (1.73 to 69 μg/kg) was administered to cancer patients, the area under the serum concentration-time curves increased proportional to the dose. Serum concentrations of filgrastim were found to decrease in paediatric cancer patients who were dosed at 5 to 15 μg/kg/day for 10 days. The decrease of serum concentrations may be associated with a change in the clearance of filgrastim due to increasing neutrophil counts.

SC injections of filgrastim solutions containing either sorbitol or mannitol resulted in similar pharmacokinetic profiles and response in ANC. When a single 5 μg/kg SC dose was administered to normal subjects using 3 concentrations of filgrastim solution (300, 600 and

960 µg/mL), the 3 concentrations were found to be equivalent in elevating ANC. Although increased maximum serum concentration and area under the serum concentration curve were observed with increasing filgrastim concentrations, these pharmacokinetic differences did not correlate with biological response.

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 IV and SC administration of single 10 µg/kg doses of Nivestim and Neupogen.

	Mean $AUC_{0\text{-}tlast}$, 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) SC 5 µg/kg and 10 µg/kg doses of Nivestim and Neupogen were as follows.

	Mean $AUC_{0\text{-}tlast}$, pg.h/mL			
Dose Group	Nivestim	Neupogen	Ratio	90% CI
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

	Mean C_{max}, pg/mL			
Dose Group	Nivestim	Neupogen	Ratio	90% CI
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

5.3 Preclinical safety data

Cell proliferation potential

As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro*, and similar effects may be seen on some non-myeloid cells *in vitro*.

Genotoxicity

In either the presence or absence of a drug enzyme metabolising system, filgrastim failed to induce chromosomal aberrations (in Chinese hamster lung cells *in vitro*) or bacterial gene mutations. Filgrastim was negative in an *in vivo* mouse micronuclear test. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolising enzyme system.

Carcinogenicity

The carcinogenic potential of filgrastim has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid

Polysorbate 80

Sodium hydroxide

Sorbitol

Water for Injections

6.2 Incompatibilities

Nivestim should not be diluted with sodium chloride solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials unless it is diluted in 5% glucose solution (see Section 4.2 Dose and method of administration, Dilution).

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and method of administration.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Diluted Nivestim should not be prepared more than 24 hours before administration and should be stored in the refrigerator at 2° to 8°C. To reduce microbiological hazard, the solution should be administered as soon as practicable after dilution.

6.4 Special precautions for storage

Nivestim should be stored in the refrigerator at 2° to 8°C. Keep Nivestim in its outer carton in order to protect from light. Prior to injection, Nivestim may be allowed to reach room temperature. Avoid vigorous shaking.

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. Accidental exposure to freezing temperatures for up to 24 hours does not affect the stability of Nivestim. The frozen pre-filled 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.

6.5 Nature and contents of container

Nivestim 120 µg/0.2 mL syringe for SC or IV injection: Single use, preservative-free syringes containing 120 µg (0.2 mL) of filgrastim (600 µg/mL). Single pack, box of 5 and box of 10.

Nivestim 300 µg/0.5 mL syringe for SC or IV injection: Single use, preservative-free syringes containing 300 µg (0.5 mL) of filgrastim (600 µg/mL). Single pack, box of 5 and box of 10.

Nivestim 480 µg/0.5 mL syringe for SC or IV injection: Single use, preservative-free syringes containing 480 µg (0.5 mL) of filgrastim (960 µg/mL). Single pack, box of 5 and box of 10.

Each pre-filled syringe is affixed with a needle closed by a needle cover that contains epoxyprene, a derivative of natural rubber latex which may come into contact with the needle.

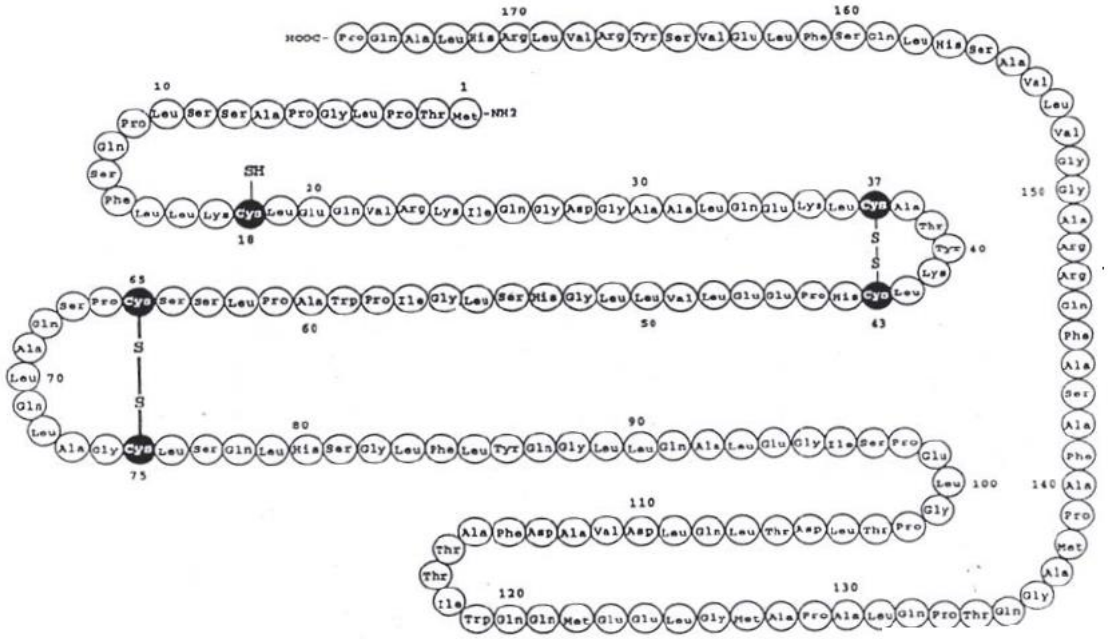
6.6 Special precautions for disposal

Product is for single use in one patient only. Discard any residue.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

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



CAS number

121181-53-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
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Toll Free number: 1800 675 229
www.pfizermedinfo.com.au

9. DATE OF FIRST APPROVAL

08 September 2011

10. DATE OF REVISION

5 May 2023

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.8	Addition of safety information on extramedullary haematopoiesis
8	Update of sponsor website