NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Zarzio® 300 microgram/0.5 mL solution for injection pre-filled syringe

Zarzio® 480 microgram/0.5 mL solution for injection pre-filled syringe

Zarzio® is a biosimilar medicine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Filled volume	Total content of active	Concentration
0.5 mL	0.3 mg	600 micrograms/mL
0.5 mL	0.48 mg	960 micrograms/mL

Each pre-filled syringe of Zarzio contains 300 micrograms (equivalent to 30 million units) or 480 micrograms (equivalent to 48 million units) of filgrastim in 0.5 mL of solution for injection.

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.

Excipients with known effect:

This medicine contains 25 mg sorbitol in each 300 and 480 microgram prefilled syringe.

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

Filgrastim is a biosimilar medicine. Prior to dispensing Zarzio the prescribing physician should review the bioequivalence data (see section 5) to determine whether Zarzio is interchangeable with the reference medicine filgrastim (rbe) marketed in New Zealand. For further information refer to http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Established Cytotoxic Chemotherapy

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

Peripheral Blood Progenitor Cell Mobilisation (PBPC)

Zarzio 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 Zarzio is indicated in patients, children or adults, with severe congenital, cyclic or idiopathic neutropenia with an Absolute Neutrophil Count (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.

HIV Infection

Zarzio is indicated for the treatment of persistent neutropenia (ANC $\leq 1.0 \times 10^9$/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

Zarzio is a biosimilar medicinal product. The prescribing physician should be involved in any decision regarding interchangeability with other products. Additional information is available on the following website (http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp).

Zarzio 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.

Established Cytotoxic Chemotherapy

Dose

The recommended dose of Zarzio is 5 microgram/kg/day. The first dose of Zarzio should not be administered less than 24 hours following cytotoxic chemotherapy.

Daily dosing with Zarzio 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 Zarzio therapy. However, for a sustained therapeutic response, Zarzio therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of Zarzio therapy, prior to the time of the expected neutrophil nadir, is not recommended.

Method of administration

Zarzio may be given as a daily SC injection or as a daily IV infusion diluted in 5% glucose solution given over 30 minutes (see Section 6.6 Special precaution for disposal - 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.

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of Zarzio is 10 microgram/kg/day. The first dose of Zarzio should not be administered less than 24 hours following cytotoxic chemotherapy but within 24 hours of bone marrow infusion.

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

Neutrophil count	**Filgrastim dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 5 mcg/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	

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

Method of administration

Zarzio may be given as a 30-minute or 24-hour IV infusion or 10 microgram/kg/day given by continuous 24-hour SC infusion. Zarzio should be diluted in 20 mL of 5% glucose solution (see Section 6.6 Special precaution for disposal - Instructions for dilution).

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

Dose

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

The recommended dose of Zarzio for PBPC mobilisation after myelosuppressive chemotherapy is 5 microgram/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.

Method of administration

Zarzio may be given as a 24-hour SC continuous infusion or a single daily SC injection. For infusions, Zarzio should be diluted in 20 mL of 5% glucose solution (see Section 6.6 Special precaution for disposal - Instructions for dilution).

Mobilisation of PBPC in normal donors prior to allogeneic PBPC transplantation

Dose

For PBPC mobilisation in normal donors, Zarzio should be administered at 10 microgram/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 have not been assessed in normal donors < 16 years or > 60 years.

Method of administration

Zarzio should be given by SC injection.

Severe Chronic Neutropenia (SCN)

Dose

Congenital neutropenia: The recommended starting dose is 12 microgram/kg/day as a single dose or in divided doses.

Idiopathic or cyclic neutropenia: The recommended starting dose is 5 microgram/kg/day as a single dose or in divided doses.

Dose adjustment: Zarzio 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 microgram/kg/day.

The long-term safety of filgrastim administration above 24 microgram/kg/day in patients with severe chronic neutropenia has not been established.

Method of administration

Congenital neutropenia, idiopathic or cyclic neutropenia, Zarzio should be given by SC injection.

HIV Infection

Dose

For reversal of neutropenia

The recommended starting dose of Zarzio is 1 microgram/kg/day given daily with titration up to a maximum of 4 microgram/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 microgram/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 microgram/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 $> 2.0 \times 10^9$/L. In clinical studies, dosing with 300 microgram/day on 1 to 7 days per week was required to maintain the ANC $> 2.0 \times 10^9$/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC $> 2.0 \times 10^9$/L.

Method of administration

Reversal of neutropenia or maintaining normal neutrophil counts: Zarzio should be given by SC injection.

Special populations

- Elderly population

  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.

- 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.

Paediatric population

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

4.3. CONTRAINDICATIONS

Zarzio should not be administered to patients with known hypersensitivity to *E. coli*-delivered proteins, filgrastim or to any of the excipients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Cases of splenic rupture have been reported following administration of filgrastim G-CSFs. 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.

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 splenomegaly 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 disease. Physicians should use caution when prescribing filgrastim in patients with sickle cell trait or sickle cell disease.

Thrombocytopenia

Thrombocytopenia has been reported commonly in patients receiving filgrastim. Platelet counts should be monitored closely.

Capillary Leak Syndrome

Capillary leak syndrome, characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration, has been reported very rarely. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate medical attention.

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.

Acute Respiratory Distress Syndrome

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 of adult respiratory distress syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given.

Glomerulonephritis

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

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 in patients receiving filgrastim and may present with generalized signs and symptoms such as fever and increased inflammatory markers. Consider aortitis in patients who develop these signs and symptoms without known aetiology.

Excipients

Filgrastim contains sorbitol as an excipient at a concentration of 50 mg/mL. It is unlikely that as a consequence of treatment with filgrastim alone that sufficient sorbitol will be infused to result in clinically relevant toxicity in affected individuals. However, in cases of HFI (Heredity Fructose Intolerance) caution is advised.

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*.

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

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 microgram/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 mobilization 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 $< 100 \times 10^9$/L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, two cases of platelets $< 50 \times 10^9$/L were reported and attributed to the leukapheresis procedure.

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

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

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

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

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.

Special precautions in recipients of allogeneic PBPC mobilised with filgrastim

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

Special precautions in patients with Severe Chronic Neutropenia (SCN)

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 severe chronic neutropenia 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 severe chronic neutropenia 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, e.g. 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. Splenomegaly 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 splenomegaly, 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 urinalysis should be performed to monitor this event.

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

Special Precautions in Patients with HIV Infection

Blood cell counts

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 microgram/day of filgrastim, there can be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples are taken for ANC measurement immediately prior to any scheduled dosing with filgrastim.

Risk associated with increased doses of myelosuppressive 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 Blood cell counts 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.

Latex-sensitive individuals

The needle shield of filgrastim contains a derivative of natural rubber latex. Although no natural rubber latex is detected in the needle shield, the safe use of filgrastim in latex-sensitive individuals has not been studied.

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.

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

65% 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.

Effects on laboratory tests

Immunogenicity

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

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.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

The potential for pharmacodynamic interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be 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

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.

Breast-feeding

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 Preclinical safety data)

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on ability to drive and use machines have been reported.

4.8. UNDESIRABLE EFFECTS

Summary of safety profile

Bone pain and pain in extremity occurred at a higher incidence in fligrastim-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, hypoaethesia, paraesthesia, insomnia, erythema and transfusion reaction.

Uncommon (≥ 1/1000 and < 1/100) hypersensitivity, lung infiltration and rash maculo-papular.

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

In normal donors undergoing PBPC mobilization 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 mobilization in normal donors, SCN patients and patients with HIV, reflecting different adverse reactions in these populations.

Cancer patients

Frequency	Body System	Undesirable Effect
Very Common (> 10%)	Gastrointestinal disorders	Nausea Vomiting
	Investigations	Blood gamma-glutamyl-transferase (GGT) increased Blood alkaline phosphatase increased Blood lactate dehydrogenase increased Blood uric acid increased
Common (1 – 10%)	General disorders and administration site condition	Fatigue Asthenia Mucosal inflammation
	Nervous system disorders	Headache
	Gastrointestinal disorders	Constipation Diarrhoea
	Metabolic and nutrition disorders	Anorexia
	Musculoskeletal disorders	Chest pain Musculoskeletal pain
	Respiratory disorders	Haemoptysis Cough Pharyngolaryngeal pain
	Skin and subcutaneous tissue disorders	Alopecia Skin rash
Uncommon (< 1%)	General disorders and administration site condition	Pain
	Respiratory disorder	Pulmonary haemorrhage
Very Rare (< 0.01%)	Immune system disorders	Allergic reaction
	Musculoskeletal disorders	Rheumatoid arthritis exacerbation
	Respiratory disorders	Lung infiltration
	Skin and subcutaneous disorders	Acute febrile neutrophilic dermatosis

Frequency	Body System	Undesirable Effect
	Renal and urinary disorders	Cutaneous vasculitis Urinary abnormalities

In normal donors undergoing PBPC mobilisation

Frequency	Body System	Undesirable Effect
Very Common (> 10%)	Nervous system disorders Blood and lymphatic system disorders Musculoskeletal disorders	Headache Leukocytosis Thrombocytopenia Musculoskeletal pain
Common (1 – 10%)	Investigations Blood and lymphatic system disorders	Blood alkaline phosphatase increased Blood lactate dehydrogenase increased Splenomegaly
Uncommon (< 1%)	Immune System disorders Blood and lymphatic system Disorders Investigations Metabolic and nutrition disorders	Severe allergic reaction Spleen disorder Serum glutamic-oxaloacetic-transaminase (SGOT) increased Hyperuricaemia
Very rare (< 0.01%)	Respiratory disorders Musculoskeletal disorders	Haemoptysis Lung infiltration Rheumatoid arthritis exacerbation

Patients with SCN

Frequency	Body System	Undesirable Effect
Very Common (> 10%)	Blood and lymphatic system disorders Investigations Metabolic and nutrition disorders	Anaemia Splenomegaly Decreased glucose Blood alkaline phosphatase increased Blood lactate dehydrogenase increased Hyperuricaemia

Frequency	Body System	Undesirable Effect
	Musculoskeletal disorders	Musculoskeletal pain
Common (1 – 10%)	Nervous system disorders	Headache
	Gastrointestinal disorders	Diarrhoea
	Hepatobiliary disorders	Hepatomegaly
	Musculoskeletal disorders	Osteoporosis
	Skin and subcutaneous disorders	Alopecia Rash Cutaneous vasculitis
	Blood and lymphatic system disorders	Thrombocytopenia
	General disorders and administration site condition	Injection site pain
Uncommon (< 1%)	Renal and urinary disorders	Haematuria Proteinuria
	Blood and lymphatic system disorders	Spleen disorders

Patients with HIV

Frequency	Body System	Undesirable Effect
Very Common (> 10%)	Musculoskeletal disorders	Musculoskeletal pain Bone pain Myalgia
Common (1 – 10%)	Blood and lymphatic disorders	Splenomegaly

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.

Description of selected adverse reactions

Allergic reactions

Allergic-type reactions, including anaphylactic reactions, skin 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 insterstitial 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 Special warnings and precautions for use).

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 leukapharesis was observed in 35% of donors.

Adverse reactions 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.

Reporting suspected adverse effects

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://nzphvc.otago.ac.nz/reporting/.

4.9. OVERDOSE

The effects of filgrastim overdose have not been established.

Doses up to 138 microgram/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

Filgrastim (recombinant-methionyl human granulocyte colony-stimulating factor, r-metHuG-CSF, from E. coli K12) is a highly purified non-glycosylated protein comprising 175 amino acids.

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

Human granulocyte colony-stimulating factor is a glycoprotein, which regulates the production and release of functional neutrophils from the bone marrow. Zarzio 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 PBPC may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation.

Infusion of PBPC 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 Zarzio with Neupogen

In vivo study [Study number: EP06-004] was conducted to investigate the pharmacodynamics properties of Zarzio in comparison with the reference product, Neupogen. Both products were tested in normal and neutropenic rats, following subcutaneous (SC) administration, a similar dose-dependent increase in the neutrophils counts and absolute neutrophil count (ANC) recovery were observed for both Zarzio and Neupogen.

A good local and systemic tolerance was observed for both products in all the treatment groups.

The study results demonstrated that the pharmacodynamics properties of Zarzio are comparable to Neupogen.

Table 1: Comparison of neutrophil count between treatment groups of equal strength in normal rats (N=60)

Group 1 (Test-Zarzio®)	Group 2 (Reference-Neupogen)	AUEC [cells x 10^3/L*days]		E_{max} [cells x 10^3/L]	
		Ratio*	95% CI for ratio* of means	Ratio*	95% CI for ratio* of means
10 microgram/kg	10 microgram/kg	1.12	0.95 - 1.33	1.28	1.08 - 1.51
20 microgram/kg	20 microgram/kg	1.15	0.97 - 1.36	1.17	0.99 - 1.39
40 microgram/kg	40 microgram/kg	1.02	0.86 - 1.21	1.06	0.90 - 1.25
80 microgram/kg	80 microgram/kg	1.12	0.95 - 1.33	1.14	0.96 - 1.35
160 microgram/kg	160 microgram/kg	0.85	0.72 - 1.01	0.94	0.80 - 1.11

*ratio test / reference

Table 2: Comparison of neutrophil count between treatment groups of equal strength in neutropenic rats (N=60)

Group 1 (Test-Zarzio®)	Group 2 (Reference-Neupogen)	AUEC [cells x 10^3/L*days]		E_{max} [cells x 10^3/L]	
		Ratio*	95% CI for ratio* of means	Ratio*	95% CI for ratio* of means
30 microgram/kg	30 microgram/kg	1.10	0.91 - 1.40	1.14	0.85 - 1.51
60 microgram/kg	60 microgram/kg	1.00	0.80 - 1.25	0.93	0.69 - 1.24

100 microgram/kg	100 microgram/kg	1.09	0.87 - 1.35	1.12	0.84 - 1.51

*ratio test / reference

In a repeat- dose toxicity study and toxicokinetics testing in rates, following SC administration of Zarzio 20, 100 and 500 microgram/kg/day and Neupogen 20 and 500 microgram/kg/day, demonstrated similar safety profiles of Zarzio and Neupogen.

In a 36-day single dose study in rabbits, local tolerance was assessed. Comparable local tolerability of Zarzio and Neupogen was found.

Clinical efficacy: Pharmacodynamics equivalence of Zarzio and Neupogen were assessed in healthy volunteers, following SC administration, in a single-dose phase I study and multiple-dose phase I study.

Pharmacodynamics equivalence after multiple SC administrations of Zarzio and Neupogen in two different doses (2.5 microgram/kg/day and 5 microgram/kg/day) was demonstrated in a randomized, double blind, two-way crossover study (Study number: EP06-103). Study results provided similar ANC and $CD34^+$ values.

Table 3: AUEC of absolute neutrophil count and CD34+ cells - 95% confidence intervals for the ratio of means (Study number: EP06-103) (N=56)

	$CD34^+$ (ng•h/mL)				
Parameter	**Dose (microgram/kg)**	**Zarzio**	**Neupogen**	**Ratio (%)**	**95% CI (%)**
$AUEC_{0-216hr}$	2.5	2815.1	2694.0	104.49	96.51-113.14
	5	2885.5	2898.3	98.99	86.79 -112.90

	ANC (nanogram•h/mL)				
Parameter	**Dose (microgram/kg)**	**Zarzio**	**Neupogen**	**Ratio (%)**	**95% CI (%)**
$AUEC_{0-216hr}$	2.5	4224.0	4134.5	102.16	99.49-104.91
	5	5191.8	5176.8	100.61	98.01-103.29

Equivalent pharmacodynamics was demonstrated in a randomized, double blind two-way crossover (Study number: EP06-105), in healthy volunteers, after single SC administration of 1 microgram/kg Zarzio and Neupogen. Study results provided similar ANC.

Table 4: Pharmacodynamics results of the ANC (N=24). (Study number: EP06-105)

	ANC (nanogram•h/mL)			
Parameter	**Zarzio**	**Neupogen**	**Ratio (%)**	**95% CI (%)**
$AUEC_{0-120hr}$	740.78	725.00	102.11	96.68-108.09

Clinical trials

No data available.

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 relative bioavailability was estimated based on the AUCs observed after IV administration (study EP06-102) and after SC administration study (EP06-103) of the same dose (5 microgram/kg). A single subcutaneous dose of 0.5 MU/kg (5 microgram/kg) resulted in maximum serum concentrations after a t_{max} of 4.5 ± 0.9 hours (mean ± SD). The bioavailability of Zarzio after subcutaneous injection is 59% (dose 5 microgram/kg) compared with 61% for Neupogen. The table below summarizes the corresponding results.

Estimation of the relative bioavailability based on geometric means and their ratios (single dose, 5 microgram/kg)

Zarzio			Neupogen		
AUC_{0-t} iv (EP06-102)	**AUC_{0-t} sc (EP06-103)**	**F**	**AUC_{0-t} iv (EP06-102)**	**AUC_{0-t} sc (EP06-103)**	**F**
632.1	370.3	0.59	634.2	383.7	0.61

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.

Zarzio is a biosimilar medicinal product. Based on available clinical data Zarzio has shown therapeutical equivalence to Neupogen.

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 nanogram/mL for 8 to 16 hours. The volume of distribution (Vd) in blood is approximately 150 mL/kg.

Excretion

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.

The elimination of filgrastim is non-linear with respect to dose, the serum clearance decreases with increasing dose. Filgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. However, the serum clearance increases with repeated dosing while the neutrophil count increases. The median serum elimination half-life ($t_{1/2}$) of filgrastim after single subcutaneous doses ranged from 2.7 hours (10 microgram/kg) to 5.7 hours (2.5 microgram/kg) and was prolonged after 7 days of dosing to 8.5 - 14 hours, respectively.

Comparability of Zarzio with Neupogen

Pharmacokinetic (PK) equivalence of Zarzio and Neupogen have been demonstrated in healthy volunteers, following IV and SC administration, in a single-dose phase I study and multiple-dose phase I study.

Comparability after multiple SC administrations was demonstrated in a randomized, double blind two-way crossover (Study number: EP06-101), in healthy volunteers receiving 10 g/kg/day of Zarzio®and Neupogen.

PK was assessed following a single IV administration, in a randomized, double blind two-way crossover (Study number: EP06-102), in healthy volunteers receiving 5 g/kg/day dose of Zarzio and Neupogen.

The PK parameters of the studies are summarised below.

Table 5: Pharmacokinetic analysis across phase I studies (Study number: EP06-101) (N=40)

Parameter	Zarzio	Neupogen	Ratio (%)	90% CI (%)
$AUC_{0\text{-}24h,sd}$ (ng•h/mL)	839.7	908.1	93.13	88.76-97.70
$AUC_{144\text{-}168h,ss}$ (nanogram•h/mL)	175.3	193.1	90.78	84.45 -97.60
$C_{max,0\text{-}24h,sd}$ (nanogram/mL)	97.7	110.3	88.84	82.49-95.67
$C_{max,144\text{-}216h,ss}$ (nanogram/mL)	35.0	39.1	89.68	81.83-98.28

Table 6: Pharmacokinetic analysis across phase I studies (Study number: EP06-102) (N=26)

Parameter	Zarzio	Neupogen	Ratio (%)	90% CI (%)
$AUC_{0\text{-}36h,sd}$	632.1	634.2	99.68	96.94 - 102.47
$C_{max,0\text{-}36h,sd}$	186.4	188.7	98.82	95.76-101.98

The results show that the Pharmacokinetic profile of Zarzio was comparable to Neupogen after IV and SC administration.

Pharmacokinetics in special populations

Paediatrics

The pharmacokinetics of filgrastim in paediatric patients after chemotherapy is similar to those in adults receiving the same weight-normalized 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.

Comparability of Zarzio with Neupogen

An open, single-arm, multi-center, phase III study (study number; EP06-301) was conducted in patients with breast cancer receiving treatment with combination chemotherapy of doxorubicin and docetaxel.

170 subjects were treated with 4 chemotherapy cycles; the mean dose by body weight administered was 6.14 ± 0.87 microgram/kg per day. The highest and the lowest doses adjusted to body weight were 3.69 and 8.42 microgram/kg, respectively.

Severe neutropenia was observed for 46% of patients in cycle 1, and 15-21% of patients in cycles 2, 3, and 4. The duration of severe neutropenia and the time to neutrophil recovery were approximately 2 days in each treatment cycle. The incidence (95% CI) for febrile neutropenia in the first treatment cycle was 5.9% (2.9%, 10.6%).

The study demonstrated efficacy of Zarzio in terms of the reduction of the incidence and duration of severe neutropenia in breast cancer patients receiving chemotherapy with a high risk for neutropenia. Zarzio efficacy profile was comparable with published data for the reference product Neupogen.

None of patients developed anti-G-CSF antibodies at any point during the study.

The study results also confirmed a comparable safety profile of Zarzio and Neupogen.

Incidence and duration of severe neutropenia in study EP06-301

			Duration of Severe Neutropenia[1]	
		Incidence	**Recovery to ANC ≥ $1.0x10^9$/L[2]**	**Consecutive Days[3]**
Cycle	**N**	**n (%)**	**Mean ± SD**	**Mean ± SD**
1	170	80 (47.1%)	2.2 ± 0.9	1.8 ± 1.4
2	162	25 (15.4%)	1.8 ± 0.6	1.3 ± 0.5
3	159	33 (20.8%)	1.9 ± 0.9	1.4 ± 0.6
4	154	27 (17.5%)	2.1 ± 0.8	1.7 ± 0.6

[1] Includes only patients who experienced severe neutropenia.

[2] Duration defined as the number of days from the first day with ANC < $0.5x10^9$/L to the first day with ANC ≥ $1.0x10^9$/L.

[3] Duration was the number of consecutive days with ANC < $0.5x10^9$/L during the treatment cycle.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

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.

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 metabolizing 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.

Impairment of fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

The pre-filled syringes also contain glutamic acid, sorbitol, polysorbate 80, sodium hydroxide (for pH adjustment), water for injections.

6.2. INCOMPATIBILITIES

Filgrastim should not be diluted with saline solutions. If required, filgrastim may be diluted in 5% glucose.

Diluted filgrastim may be adsorbed to glass and plastic materials. However, when diluted in 5% glucose solution, filgrastim is compatible with glass and a variety of plastic including PVC (polyvinyl chloride), polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

Filgrastim pre-filled syringes are for single-dose use only.

6.3. SHELF LIFE

Shelf life is 36 months.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Filgrastim should be stored in a refrigerator at 2 – 8ºC. Brief accidental exposure to freezing temperatures does not adversely affect the stability of filgrastim.

For the purpose of ambulatory use, the product can be removed from the refrigerator and stored at room temperature (not above 25°C) for one single period of up to 72 hours. At the end of this period, the product should not be put back in the refrigerator and should be disposed of.

This medicine should not be used after the expiry date (EXP) shown on the pack.

For storage of diluted solutions, see Instructions for handling, *below*.

6.5. NATURE AND CONTENTS OF CONTAINER

Zarzio® 300 microgram (30 MU) in 0.5 mL pre-filled syringe pack of 1, 3, 5 and 10.

Zarzio® 480 microgram (48 MU) in 0.5 mL pre-filled syringe pack of 1, 3, 5 and 10.

Not all presentations may be marketed in New Zealand.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Instructions for handling

Avoid vigorous shaking.

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

Filgrastim pre-filled syringes are for single use only.

Instructions for Dilution

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

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

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

When diluted in glucose 5% solution, filgrastim is compatible with glass and a variety of plastics including polyvinylchloride, polyolefin (a copolymer of polypropylene and polyethylene) and polypropylene. Diluted filgrastim solutions should not be prepared more than 24 hours before administration and should also be stored refrigerated at 2 - 8ºC.

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

Using the pre-filled syringe with a needle safety guard

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket

AUCKLAND 1149

Telephone: 0800 354 335

9. DATE OF FIRST APPROVAL

24 May 2012

10. DATE OF REVISION OF THE TEXT

09/09/2021

NEW ZEALAND DATA SHEET

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of MDS/AML in breast and lung cancer patients
4.8	Addition of MDS/AML in breast and lung cancer patients