

1. NAME OF THE MEDICINAL PRODUCT

Zarzio 30 MU/0.5 ml solution for injection or infusion in pre-filled syringe

Zarzio 48 MU/0.5 ml solution for injection or infusion in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zarzio 30 MU/0.5 ml solution for injection or infusion in pre-filled syringe:

Each ml of solution contains 60 million units (MU) [equivalent to 600 micrograms (μg)] filgrastim*.

Each pre-filled syringe contains 30 MU (equivalent to 300 μg) filgrastim in 0.5 ml.

Zarzio 48 MU/0.5 ml solution for injection or infusion in pre-filled syringe:

Each ml of solution contains 96 million units (MU) [equivalent to 960 micrograms (μg)] filgrastim*.

Each pre-filled syringe contains 48 MU (equivalent to 480 μg) filgrastim in 0.5 ml.

* recombinant methionylated human granulocyte-colony stimulating factor (G-CSF) produced in *E. coli* by recombinant DNA technology.

Excipient: Each ml of solution contains 50 mg sorbitol (E420).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion in pre-filled syringe

Clear, colourless to slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- 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 reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

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

- Mobilisation of peripheral blood progenitor cells (PBPC).
- In children and adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9/\text{l}$, and a history of severe or recurrent infections, long term administration of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

- Treatment of persistent neutropenia ($ANC = 1.0 \times 10^9/l$) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other therapeutic options are inappropriate.

4.2 Posology and method of administration

Filgrastim 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.

Zarzio is available in strengths of 30 MU/0.5 ml and 48 MU/0.5 ml.

Established cytotoxic chemotherapy

The recommended dose of filgrastim is 0.5 MU/kg/day (5 µg/kg/day). The first dose of filgrastim should not be administered less than 24 hours following cytotoxic chemotherapy.

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

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

Patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of filgrastim is 1.0 MU/kg/day (10 µg/kg/day). The first dose of filgrastim should not be administered less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow infusion.

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

Absolute neutrophil count	Filgrastim dose adjustment
ANC > $1.0 \times 10^9/l$ for 3 consecutive days	Reduce to 0.5 MU/kg/day (5 µg/kg/day)
Then, if ANC remains > $1.0 \times 10^9/l$ for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < $1.0 \times 10^9/l$ during the treatment period, the dose of filgrastim should be re-escalated according to the above steps	

Mobilisation of PBPC

Patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU/kg/day (10 µg/kg/day) for 5 - 7 consecutive days. Timing of leukapheresis:

1 or 2 leukaphereses on days 5 and 6 are often sufficient. In other circumstances, additional leukaphereses may be necessary. Filgrastim dosing should be maintained until the last leukapheresis.

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

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 means 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.

Normal donors prior to allogeneic PBPC transplantation

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

Severe chronic neutropenia (SCN)

Congenital neutropenia

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

Idiopathic or cyclic neutropenia

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

Dose adjustments

Filgrastim should be administered daily until the neutrophil count has reached and can be maintained at more than $1.5 \times 10^9/l$. 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 1 - 2 weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently the dose may be individually adjusted every 1 - 2 weeks to maintain the average neutrophil count between $1.5 \times 10^9/l$ and $10 \times 10^9/l$. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical studies, 97% of patients who responded had a complete response at doses of = 2.4 MU/kg/day (24 µg/kg/day). The long-term safety of filgrastim administration above 2.4 MU/kg/day (24 µg/kg/day) in patients with SCN has not been established.

HIV infection

Reversal of neutropenia

The recommended starting dose of filgrastim is 0.1 MU/kg/day (1 µg/kg/day) given daily with titration up to a maximum of 0.4 MU/kg/day (4 µg/kg/day) until a normal neutrophil count is reached and can be maintained (ANC $> 2.0 \times 10^9/l$). In clinical studies, $> 90\%$ 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 1.0 MU/kg/day (10 µg/kg/day) were required to achieve reversal of neutropenia.

Maintenance of normal neutrophil counts

When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU/day (300 µg/day) is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at $> 2.0 \times 10^9/l$. In clinical studies, dosing with 30 MU/day (300 µg/day) on 1 - 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 $> 2.0 \times 10^9/l$.

Special populations

Patients with renal/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 patients in the SCN and cancer settings

In clinical studies 65% of patients treated for SCN were younger than 18 years. For this age-group, which mostly includes patients with congenital neutropenia, efficacy was proven. There were no differences in the safety profiles for paediatric patients treated for SCN in comparison to adults.

Data from clinical studies in paediatric patients indicate that the safety and efficacy of filgrastim are similar in both adults and children receiving cytotoxic chemotherapy.

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

Elderly patients

In clinical investigations with filgrastim a small number of elderly patients was included. No specific studies have been performed for this patient population. Therefore, specific posology recommendations for these patients cannot be made.

Method of administration

Established cytotoxic chemotherapy

Filgrastim may be administered as a daily subcutaneous injection or alternatively as a daily intravenous infusion over 30 minutes. For further instructions on dilution with glucose 50 mg/ml (5%) solution prior to infusion see section 6.6. The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance. In randomised clinical studies, a subcutaneous dose of 23 MU/m²/day (230 µg/m²/day) or rather 0.4 - 0.84 MU/kg/day (4 - 8.4 µg/kg/day) was used.

Patients treated with myeloablative therapy followed by bone marrow transplantation

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

Mobilisation of PBPC

Subcutaneous injection.

For the mobilisation of PBPC in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation the recommended dose of filgrastim may also be administered as a 24 hour subcutaneous continuous infusion. For infusions filgrastim should be diluted in

20 ml of glucose 50 mg/ml (5%) solution. For further instructions on dilution with glucose 50 mg/ml (5%) solution prior to infusion see section 6.6.

SCN/HIV infection

Subcutaneous injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Special warnings

Filgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established posology regimens (see below).

Filgrastim should not be administered to patients with severe congenital neutropenia (Kostmann's syndrome) with abnormal cytogenetics (see below).

Established cytotoxic chemotherapy

Malignant cell growth

Since investigations showed that G-CSF can promote growth of myeloid cells *in vitro* the following warnings should be considered.

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

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.

Leucocytosis

White blood cell counts of $100 \times 10^9/l$ or greater have been observed in less than 5% of patients receiving filgrastim at doses above 0.3 MU/kg/day (3 $\mu\text{g}/\text{kg}/\text{day}$). No undesirable effects directly attributable to this degree of leucocytosis have been reported. However, in view of the potential risks associated with severe leucocytosis, a white blood cell count should be performed at regular intervals during filgrastim therapy. If leukocyte counts exceed $50 \times 10^9/l$ after the expected nadir, filgrastim should be discontinued immediately. However, during the period of administration of filgrastim for PBPC mobilisation, it should be discontinued or its dose should be reduced if the leukocyte counts rise to $> 70 \times 10^9/l$.

Risks associated with increased doses of chemotherapy

Special caution should be used when treating patients with high-dose chemotherapy because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic, and dermatologic effects (please refer to the Summary of Product Characteristics 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 on the prescribed schedule) the patient may be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

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

Other special precautions

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

There have been reports of Graft versus Host Disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 5.1).

Mobilisation of PBPC

Prior exposure to cytotoxic agents

Patients who have undergone very extensive prior myelosuppressive therapy, followed by administration of filgrastim for mobilisation of PBPCs, may not show sufficient mobilisation of these blood cells to achieve the recommended minimum yield ($= 2.0 \times 10^6$ CD34+ cells/kg) or acceleration of platelet recovery to the same degree.

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

Assessment of progenitor cell yields

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

Statistical analysis of the relationship between the number of CD34+ cells re-infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship. The recommendation of a minimum yield of $= 2.0 \times 10^6$ CD34+ cells/kg is based on published experience resulting in adequate haematologic reconstitution. Yields in excess of this minimum yield appear to correlate with more rapid recovery, those below with slower recovery.

Normal donors 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.

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

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 posology should be reduced if the leukocyte counts rise to > $70 \times 10^9/l$.

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

Transient cytogenetic modifications have been observed in normal donors following G-CSF use. The significance of these changes is unknown.

Long-term safety follow-up of donors is ongoing. Nevertheless, a risk of promotion of a malignant myeloid clone can not be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors for at least 10 years to ensure monitoring of long-term safety.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported in healthy donors and patients following administration of G-CSFs. Some cases of splenic rupture were fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal pain or shoulder tip pain.

In normal donors, pulmonary adverse events (haemoptysis, pulmonary haemorrhage, pulmonary infiltrates, dyspnoea and hypoxia) have been reported very rarely in post marketing experience. In case of suspected or confirmed pulmonary adverse events, discontinuation of treatment with filgrastim should be considered and appropriate medical care given.

Recipients of allogeneic PBPCs mobilised with filgrastim

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

SCN

Blood cell counts

Platelet counts should be monitored closely, especially during the first few weeks of filgrastim therapy. Consideration should be given to intermittent cessation or decreasing the dose of filgrastim in patients who develop thrombocytopenia, i.e. platelets consistently < $100,000/mm^3$.

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

Transformation to leukaemia or myelodysplastic syndrome

Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders such as aplastic anaemia, myelodysplasia, and myeloid leukaemia. Complete blood cell counts

with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment.

There was a low frequency (approximately 3%) of myelodysplastic syndromes (MDS) or leukaemia in clinical study patients with SCN treated with filgrastim. This observation has only been made in patients with congenital neutropenia. MDS and leukaemias are natural complications of the disease and are of uncertain relation to filgrastim therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. If patients with SCN develop abnormal cytogenetics, the risks and benefits of continuing filgrastim should be carefully weighed; Filgrastim should be discontinued if MDS or leukaemia occurs. It is currently unclear whether long-term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions

Causes of transient neutropenia, such as viral infections should be excluded.

Splenic enlargement is a direct effect of treatment with filgrastim. 31% of patients in studies were documented as having palpable splenomegaly. Increases in volume, measured radiographically, occurred early during Filgrastim therapy and tended to plateau. Dose reductions were noted to slow or stop the progression of splenic enlargement, and in 3% of patients a splenectomy was required. Spleen size should be evaluated regularly. Abdominal palpation should be sufficient to detect abnormal increases in splenic volume.

Haematuria/proteinuria occurred in a small number of patients. Regular urine analyses should be performed to monitor this event.

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

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 2 weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU/day (300 µg/day) of filgrastim, there can be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is recommended that blood samples are taken for ANC measurement immediately prior to any scheduled dosing with filgrastim.

Risk associated with increased doses of myelosuppressive medicinal products

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

Infections and malignancies causing myelosuppression

Neutropenia may be due to bone marrow-infiltrating opportunistic infections such as Mycobacterium avium complex or malignancies such as lymphoma. In patients with known bone marrow-infiltrating infections or malignancy, consider appropriate therapy for treatment of the underlying condition in

addition to administration of filgrastim for treatment of neutropenia. The effects of filgrastim on neutropenia due to bone marrow-infiltrating infection or malignancy have not been well established.

Other special precautions

Rare pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration (see section 4.8). Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given in these cases.

Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with filgrastim for more than 6 months.

Sickle cells crises, in some cases fatal, have been reported with the use of filgrastim in subjects with sickle cell disease. Physicians should exercise caution when considering the use of filgrastim in patients with sickle cell disease, and only after careful evaluation of the potential risks and benefits.

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

Excipients

Zarzio contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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 Pregnancy and lactation

There are no adequate data from the use of filgrastim in pregnant women. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. 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.

In pregnancy, the possible risk of filgrastim use to the foetus must be weighed against the expected therapeutic benefit.

It is not known whether filgrastim is excreted in human milk, therefore it is not recommended for use in breast-feeding women.

4.7 Effects on ability to drive and use machines

Filgrastim has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported adverse reactions to filgrastim are mild to moderate musculoskeletal pain occurring in more than 10% of patients. Musculoskeletal pain is usually controlled with standard analgesics.

Adverse reactions listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common (= 1/10), common (= 1/100 to < 1/10), uncommon (= 1/1,000 to < 1/100), rare (= 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1. Adverse reactions in clinical trials in cancer patients

Immune system disorders	
Very rare:	Allergic-type reactions*, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypotension
Vascular disorders	
Uncommon:	Hypotension (transient)
Rare:	Vascular disorders* including venoocclusive disease and fluid volume disturbances
Respiratory, thoracic and mediastinal disorders	
Very rare:	Pulmonary oedema*, interstitial pneumonia*, pulmonary infiltrates*
Skin and subcutaneous tissue disorders	
Very rare:	Sweet's Syndrome*, cutaneous vasculitis
Musculoskeletal, connective tissue and bone disorders	
Very common:	Musculoskeletal pain (mild or moderate)
Common:	Musculoskeletal pain (severe)
Very rare:	Rheumatoid arthritis exacerbation
Renal and urinary disorders	
Very rare:	Micturition disorders (predominantly dysuria)
Investigations	
Very common:	Blood alkaline phosphatase, blood lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT) and blood uric acid increased (reversible, dose-dependent, mild or moderate)

* see below

Table 2. Adverse reactions in clinical trials in normal donors undergoing PBPC mobilisation

Immune system disorders	
Uncommon:	Severe allergic reaction: anaphylaxis, angioedema, urticaria, rash

Blood and the lymphatic system disorders	
Very common:	Leucocytosis (WBC > 50 x 10 ⁹ /l), thrombocytopenia (platelets < 100 x 10 ⁹ /l; transient)
Common:	Splenomegaly (generally asymptomatic, also in patients)
Uncommon:	Spleen disorder
Very rare:	Splenic rupture (also in patients)

Nervous system disorders	
Very common:	Headache

Respiratory, thoracic and mediastinal disorders	
Very rare:	Haemoptysis*, pulmonary haemorrhage*, pulmonary infiltrates*, dyspnoea*, hypoxia*

Musculoskeletal, connective tissue and bone disorders	
Very common:	Musculoskeletal pain (mild to moderate, transient)
Uncommon:	Rheumatoid arthritis and arthritic symptoms exacerbation

Investigations	
Common:	Blood alkaline phosphatase and LDH increased (transient, minor)
Uncommon:	Aspartate aminotransferase (AST) and blood uric acid increased (transient, minor)

* see below

Table 3. Adverse reactions in clinical trials in SCN patients

Blood and the lymphatic system disorders	
Very common:	Anaemia, splenomegaly (may be progressive in a minority of cases)
Common:	Thrombocytopenia
Uncommon:	Spleen disorder

Nervous system disorders	
Common:	Headache

Respiratory, thoracic and mediastinal disorders	
Very common:	Epistaxis

Gastrointestinal disorders	
Common:	Diarrhoea

Hepato-biliary disorders	
Common:	Hepatomegaly

Skin and subcutaneous tissue disorders	
Common:	Cutaneous vasculitis (during long term use), alopecia, rash

Musculoskeletal, connective tissue and bone disorders	
Very common:	General musculoskeletal pain, bone pain
Common:	Osteoporosis, arthralgia

Renal and urinary disorders	
Uncommon:	Haematuria, proteinuria

General disorders and administration site conditions	
Common:	Injection site pain

Investigations	
Very common:	Blood alkaline phosphatase, LDH and blood uric acid increased (transient), blood glucose decreased (transient, moderate)

Table 4. Adverse reactions in clinical trials in HIV Patients

Blood and lymphatic system disorders

Common: Spleen disorder, splenomegaly*

Musculoskeletal, connective tissue and bone disorders

Very common: Musculoskeletal pain (mild to moderate)

* see below

In randomised, placebo-controlled clinical studies, filgrastim did not increase the incidence of 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, skin rash, chest pain, generalised weakness, sore throat, constipation and unspecified pain.

Allergic reactions occurred on initial or subsequent treatment in patients receiving filgrastim. Overall, reports were more common after intravenous administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Vascular disorders have been reported in patients undergoing high dose chemotherapy followed by autologous bone marrow transplantation. The causal association with filgrastim has not been established.

Pulmonary adverse reactions have in some cases been reported with an outcome of respiratory failure or adult respiratory distress syndrome (ARDS), which may be fatal. In normal donors, pulmonary adverse events (haemoptysis, pulmonary haemorrhage, pulmonary infiltrates, dyspnoea and hypoxia) have been reported very rarely in post marketing experience (see section 4.4).

The occurrence of Sweet's syndrome (acute febrile neutrophilic dermatosis) has been reported occasionally in cancer patients. However, since a significant percentage of these patients were suffering from leukaemia, a condition known to be associated with Sweet's syndrome, a causal relationship with filgrastim has not been established.

Isolated cases of sickle cells crises have been reported in patients with sickle cell disease (see section 4.4). The frequency is not known.

In all cases of splenic enlargement in HIV patients 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.

Immunogenicity

In four clinical studies none of the healthy volunteers or cancer patients developed anti-rhG-CSF antibodies (neither binding nor neutralising) upon treatment with Zarzio.

4.9 Overdose

The effects of filgrastim overdose have not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Colony stimulating factors, ATC Code: L03AA02

Human G-CSF 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 SCN patients filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 - 2 days, and to normal levels within 1 - 7 days. As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells, which have specific receptors for G-CSF. Accordingly, G-CSF has been shown to induce endothelial cell functions related to angiogenesis. Additionally, G-CSF has been shown to increase neutrophil migration across the vascular endothelium.

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

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

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

Relative Risk (95% CI) of GvHD and TRM Following treatment with G-CSF after bone marrow transplantation					
Publication	Period of Study	N	Acute Grade II - IV GvHD	Chronic GvHD	TRM
Meta-Analysis (2003)	1986 - 2001 ^a	1198	1.08 (0.87, 1.33)	1.02 (0.82, 1.26)	0.70 (0.38, 1.31)
European Retrospective Study (2004)	1992 - 2002 ^b	1789	1.33 (1.08, 1.64)	1.29 (1.02, 1.61)	1.73 (1.30, 2.32)
International Retrospective			1.11	1.10	1.26

Study (2006)	1995 - 2000 ^b	2110	(0.86, 1.42)	(0.86, 1.39)	(0.95, 1.67)
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^aAnalysis includes studies involving BM transplant during this period; some studies used GM-CSF

^bAnalysis includes patients receiving BM transplant during this period

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

In normal donors, a 1 MU/kg/day (10 µg/kg/day) dose administered subcutaneously for 4 - 5 consecutive days allows a collection of = 4 x 10⁶ CD34+ cells/kg recipient BW in the majority of the donors after two leukaphereses.

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 children or adults with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in ACNs in peripheral blood and a reduction of infection and related events.

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

5.2 Pharmacokinetic properties

Randomised, double-blind, single and multiple dose, crossover studies in 146 healthy volunteers showed that the pharmacokinetic profile of Zarzio was comparable to that of the reference product after subcutaneous and intravenous administration.

Absorption

A single subcutaneous dose of 0.5 MU/kg (5 µg/kg) resulted in maximum serum concentrations after a t_{max} of 4.5 ± 0.9 hours (mean ± SD).

Distribution

The volume of distribution in blood is approximately 150 ml/kg. Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/ml for 8 - 16 hours. There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

Elimination

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 (1.0 MU/kg, 10 µg/kg) to 5.7 hours (0.25 MU/kg, 2.5 µg/kg) and was prolonged after 7 days of dosing to 8.5 - 14 hours, respectively.

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 drug accumulation and comparable elimination half-lives.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glutamic acid
Sorbitol (E420)
Polysorbate 80
Water for injections

6.2 Incompatibilities

Zarzio must not be diluted with sodium chloride solutions.

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

Diluted filgrastim may be adsorbed to glass and plastic materials, unless it is diluted in glucose 50 mg/ml (5%) solution (see section 6.6).

6.3 Shelf life

30 months.

After dilution: Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Keep the pre-filled syringe in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Pre-filled syringe (type I glass) with injection needle (stainless steel), with or without a needle safety guard, containing 0.5 ml solution.

Pack sizes of 1, 3, 5 or 10 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution should be visually inspected prior to use. Only clear solutions without particles should be used. Accidental exposure to freezing temperatures does not adversely affect the stability of Zarzio.

Zarzio contains no preservative: In view of the possible risk of microbial contamination, Zarzio syringes are for single use only.

Dilution prior to administration (optional)

If required, Zarzio may be diluted in glucose 50 mg/ml (5%) solution.

Dilution to a final concentration < 0.2 MU/ml (2 µg/ml) is not recommended at any time.

For patients treated with filgrastim diluted to concentrations < 1.5 MU/ml (15 µg/ml), human serum albumin (HSA) should be added to a final concentration of 2 mg/ml.

Example: In a final volume of 20 ml, total doses of filgrastim less than 30 MU (300 µg) should be given with 0.2 ml of human serum albumin 200 mg/ml (20%) solution Ph. Eur. added.

When diluted in glucose 50 mg/ml (5%) solution, filgrastim is compatible with glass and a variety of plastics including polyvinylchloride, polyolefin (a copolymer of polypropylene and polyethylene) and polypropylene.

Using the pre-filled syringe with a needle safety guard

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

Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBERS

Zarzio 30 MU/0.5 ml solution for injection or infusion in pre-filled syringe

EU/1/08/495/001 – pack of 1 syringe
EU/1/08/495/002 – pack of 3 syringes
EU/1/08/495/003 – pack of 5 syringes
EU/1/08/495/004 – pack of 10 syringes

Zarzio 48 MU/0.5 ml solution for injection or infusion in pre-filled syringe

EU/1/08/495/005 – pack of 1 syringe
EU/1/08/495/006 – pack of 3 syringes

EU/1/08/495/007 – pack of 5 syringes

EU/1/08/495/008 – pack of 10 syringes

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2009

10. DATE OF REVISION OF THE TEXT

21 October 2009

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.