ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 [mcg]) filgrastim*.
Each pre-filled syringe contains 30 MU (equivalent to 300 mcg) 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 [mcg]) filgrastim*.
Each pre-filled syringe contains 48 MU (equivalent to 480 mcg) filgrastim in 0.5 mL.

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

Excipient with known effect
Each mL of solution contains 50 mg sorbitol (E420).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion in pre-filled syringe (injection or infusion).
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 (PBPCs).

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

- 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 Posology and method of administration

Filgrastim therapy should only be given in collaboration with an oncology centre which has experience in 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

Posology

The recommended dose of filgrastim is 0.5 MU/kg/day (5 mcg/kg/day). The first dose of filgrastim should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 mcg/m^2/day (4.0 to 8.4 mcg/kg/day) was used.

Daily dosing with filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid 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 - 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.

Method of administration

Filgrastim may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minutes (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 patients treated with myeloablative therapy followed by bone marrow transplantation

Posology

The recommended starting dose of filgrastim is 1.0 MU/kg/day (10 mcg/kg/day). The first dose of filgrastim should be administered at least 24 hours following cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

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

Neutrophil count	**Filgrastim dose adjustment**
> 1.0×10^9/L for 3 consecutive days	Reduce to 0.5 MU/kg/day (5 mcg/kg/day)
Then, if ANC remains > 1.0×10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0×10^9/L during the treatment period, the dose of filgrastim should be re-escalated according to the above steps	
ANC = absolute neutrophil count	

Method of administration

Filgrastim may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 mL of 5% glucose solution (see section 6.6).

For the mobilisation of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation

Posology

The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU/kg/day (10 mcg/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 mcg/kg/day) 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.

Method of administration

Filgrastim for PBPC mobilisation when used alone:
Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions filgrastim should be diluted in 20 mL of 5% glucose solution (see section 6.6).

Filgrastim for PBPC mobilisation after myelosuppressive chemotherapy:
Filgrastim should be given by subcutaneous injection.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

Posology

For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU/kg/day (10 mcg/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.

Method of administration

Filgrastim should be given by subcutaneous injection.

In patients with severe chronic neutropenia (SCN)

Posology

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

Dose adjustment
Filgrastim should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than 1.5×10^9/L. When the response has been obtained, the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count. After 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 1.5×10^9/L and 10×10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97% of patients who responded had a complete response at doses ≤ 24 mcg/kg/day. The long-term safety of filgrastim administration above 24 mcg/kg/day in patients with SCN has not been established.

Method of administration

Congenital, idiopathic or cyclic neutropenia: Filgrastim should be given by subcutaneous injection.

In patients with HIV infection

Posology

For reversal of neutropenia
The recommended starting dose of filgrastim is 0.1 MU/kg/day (1 mcg/kg/day), with titration up to a maximum of 0.4 MU/kg/day (4 mcg/kg/day) until a normal neutrophil count is reached and can be maintained (ANC > 2.0×10^9/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 mcg/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 30 MU/day (300 mcg/day) is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2.0×10^9/L. In clinical studies, dosing with 30 MU/day (300 mcg/day) on 1 - 7 days per week was required to maintain the ANC > 2.0×10^9/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC > 2.0×10^9/L.

Method of administration

Reversal of neutropenia or maintaining normal neutrophil counts: Filgrastim should be given by subcutaneous injection.

Elderly

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

Renal impairment

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

Paediatric use in the SCN and cancer settings

Sixty-five percent of the 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 SCN.

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.

Posology

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

Method of administration

The pre-filled syringe is not designed to measure volumes less than 0.3 mL due to the spring mechanism. Doses of less than 0.3 mL should not be administered with this product.

If required, the solution for injection may be diluted (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of granulocyte-colony stimulating factors (G-CSFs), the name and the batch number of the administered product should be clearly recorded.

Special warnings and precautions across indications

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment has been reported in patients treated with filgrastim. Permanently discontinue Zarzio in patients with clinically significant hypersensitivity. Do not administer Zarzio to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Pulmonary adverse effects

Pulmonary adverse effects, in particular interstitial lung disease, have been reported after G-CSF administration. Patients with a recent history of lung infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of acute respiratory distress syndrome (ARDS). Filgrastim should be discontinued and appropriate treatment given in these cases.

Glomerulonephritis

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

Capillary leak syndrome

Capillary leak syndrome, which can be life-threatening if treatment is delayed, has been reported after granulocyte colony-stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see section 4.8).

Splenomegaly and Splenic rupture

Generally asymptomatic cases of splenomegaly and cases of splenic rupture have been reported in patients and normal donors following administration of filgrastim. Some cases of splenic rupture were fatal. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal pain or shoulder tip pain. Dose reductions of filgrastim have been noted to slow or stop the progression of splenic enlargement in patients with severe chronic neutropenia, and in 3% of patients a splenectomy was required.

Malignant cell growth

G-CSF can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

Myelodysplastic syndrome or Chronic myeloid leukemia

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

Acute myeloid leukaemia

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

Thrombocytopenia

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

Leukocytosis

White blood cell counts of 100×10^9/L or greater have been observed in less than 5% of cancer patients receiving filgrastim at doses above 0.3 MU/kg/day (3 mcg/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 50×10^9/L after the expected nadir, filgrastim should be discontinued immediately. When administered for PBPC mobilisation, filgrastim should be discontinued or its dosage should be reduced if the leukocyte counts rise to $> 70 \times 10^9$/L.

Immunogenicity

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

Special warning and precautions associated with co-morbidities

Special precautions in sickle cell trait and sickle cell disease

Sickle cell crises, in some cases fatal, have been reported with the use of filgrastim in patients with sickle cell trait or sickle cell disease. Physicians should use caution when prescribing filgrastim in patients with sickle cell trait or sickle cell disease.

Osteoporosis

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

Special precautions in cancer patients

Filgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

Risks associated with increased doses of chemotherapy

Special caution should be used when treating patients with high-dose chemotherapy because improved 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 prescribing information of the specific chemotherapy agents used).

Effect of chemotherapy on erythrocytes and thrombocytes

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.

Myelodysplastic syndrome and acute myeloid leukaemia in patients with breast and lung cancer

In the post-marketing observational study, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) were associated with the use of pegfilgrastim, an alternative G-CSF medicinal product, in conjunction with chemotherapy and/or radiotherapy in patients with breast or lung cancer. A similar association between filgrastim and MDS/AML was not observed. Nevertheless, patients with breast or lung cancer should be monitored for signs and symptoms of MDS/AML.

Other special precautions

The effects of filgrastim in patients with substantially reduced myeloid progenitors have not been studied. Filgrastim acts primarily on neutrophil precursors to exert its effect in elevating neutrophil counts. Therefore, in patients with reduced precursors, neutrophil response may be diminished (such

as those treated with extensive radiotherapy or chemotherapy, or those with bone marrow infiltration by tumour).

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high dose chemotherapy followed by transplantation.

There have been reports of Graft versus Host Disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 4.8 and 5.1).

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

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

Special precautions in patients undergoing PBPC mobilisation

Mobilisation

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

Prior exposure to cytotoxic agents

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

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

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.

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

Special precautions in recipients of allogeneic PBPCs mobilised with filgrastim

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

Special precautions in SCN patients

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

Blood cell counts

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 trial 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 was subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. It is currently unclear whether long-term treatment of patients with SCN will predispose patients to cytogenetic abnormalities, MDS or 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.

Haematuria was common and proteinuria occurred in a small number of patients. Regular urinalysis should be performed to monitor these events.

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

Special precautions in patients with HIV infection

Blood cell counts

Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of filgrastim. It is recommended that the ANC is measured daily for the first 2 - 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 mcg/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.

Excipients

Zarzio contains sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity (see section 5.3). There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.

Zarzio is not recommended during pregnancy.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse reactions that may occur during filgrastim treatment include: anaphylactic reaction, serious pulmonary adverse events (including interstitial pneumonia and ARDS), capillary leak syndrome, severe splenomegaly/splenic rupture, transformation to myelodysplastic syndrome or

leukaemia in SCN patients, GvHD in patients receiving allogeneic bone marrow transfer or peripheral blood cell progenitor cell transplant and sickle cell crisis in patients with sickle cell disease.

The most commonly reported adverse reactions are pyrexia, musculoskeletal pain (which includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain), anaemia, vomiting, and nausea. In clinical trials in cancer patients musculoskeletal pain was mild or moderate in 10%, and severe in 3% of patients.

b. Tabulated summary of adverse reactions

The data in the tables below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	**Adverse reactions**			
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Infections and infestations		Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection		
Blood and lymphatic system disorders	Thrombocyto-penia Anaemia[e]	Splenomegaly[a] Haemoglobin decreased[e]	Leukocytosis[a]	Splenic rupture[a] Sickle cell anaemia with crisis Extramedullary hematopoiesis
Immune sys-tem disorders			Hypersensitivity Drug hypersensitivity[a] Graft versus host disease[b]	Anaphylactic reaction
Metabolism and nutrition disorders		Decreased Appetite[e] Blood lactate dehydrogenase increased	Hyperuricaemia Blood uric acid increased	Blood glucose decreased Pseudogout[a] (Chondrocalcinosis Pyro-phosphate) Fluid volume disturbances
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache[a]	Dizziness Hypoaesthesia Paraesthesia		
Vascular Disorders		Hypertension Hypotension	Veno-occlusive disease[d]	Capillary leak syndrome[a] Aortitis

MedDRA system organ class	Adverse reactions			
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Respiratory, thoracic and mediastinal disorders		Haemoptysis Dyspnoea Cough[a] Oropharyngeal pain[a, e] Epistaxis	Acute respiratory distress syndrome[a] Respiratory failure[a] Pulmonary oedema[a] Pulmonary haemorrhage Interstitial lung disease[a] Lung infiltration[a] Hypoxia	
Gastrointestinal disorders	Diarrhoea[a, e] Vomiting[a, e] Nausea[a]	Oral pain Constipation[e]		
Hepatobiliary disorders		Hepatomegaly Blood alkaline phosphatase increased	Aspartate aminotransferase increased Gamma-glutamyl transferase increased	
Skin and subcutaneous tissue disorders	Alopecia[a]	Rash[a] Erythema	Maculopapular rash	Cutaneous vasculitis[a] Sweets syndrome (acute febrile neutrophilic dermatosis)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[c]	Muscle spasms	Osteoporosis	Bone density decreased Exacerbation of rheumatoid arthritis
Renal and urinary disorders		Dysuria Haematuria	Proteinuria	Glomerulonephritis Urine abnormality
General disorders and administration site conditions	Fatigue[a] Mucosal inflammation[a] Pyrexia	Chest pain[a] Pain[a] Asthenia[a] Malaise[e] Oedema peripheral[e]	Injection site reaction	
Injury, poisoning and procedural complications		Transfusion reaction[e]		

[a] See section c (Description of selected adverse reactions)

[b] There have been reports of GvHD and fatalities in patients after allogeneic bone marrow transplantation (see section c)

[c] Includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

[d] Cases were observed in the post-marketing setting in patients undergoing bone marrow transplant or PBPC mobilisation
[e] Adverse events with higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy

c. Description of selected adverse reactions

Hypersensitivity

Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported in clinical studies and in post marketing experience. Overall, reports were more common after IV administration. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Pulmonary adverse events

In clinical studies and the post-marketing setting pulmonary adverse effects including interstitial lung disease, pulmonary oedema, and lung infiltration have been reported in some cases with an outcome of respiratory failure or acute respiratory distress syndrome (ARDS), which may be fatal (see section 4.4).

Splenomegaly and Splenic rupture

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

Capillary leak syndrome

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

Cutaneous vasculitis

Cutaneous vasculitis has been reported in patients treated with filgrastim. The mechanism of vasculitis in patients receiving filgrastim is unknown. During long term use cutaneous vasculitis has been reported in 2% of SCN patients.

Leukocytosis

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

Sweets syndrome

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

Pseudogout (chondrocalcinosis pyrophosphate)

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

GvHD

There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (see section 4.4 and 5.1).

d. Paediatric population

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, suggesting no age-related differences in the pharmacokinetics of filgrastim. The only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

There is insufficient data to further evaluate filgrastim use in paediatric subjects.

e. Other special populations

Geriatric use

No overall differences in safety or effectiveness were observed between subjects over 65 years of age compared to younger adult (> 18 years of age) subjects receiving cytotoxic chemotherapy and clinical experience has not identified differences in the responses between elderly and younger adult patients. There is insufficient data to evaluate filgrastim use in geriatric subjects for other approved filgrastim indications.

Paediatric SCN patients

Cases of decreased bone density and osteoporosis have been reported in paediatric patients with severe chronic neutropenia receiving chronic treatment with filgrastim.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The effects of filgrastim overdosage have not been established. Discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to normal levels in 1 to 7 days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, colony stimulating factors, ATC code: L03AA02

Zarzio is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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.

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 the peripheral blood. These autologous PBPCs may be harvested and infused after high-dose cytotoxic therapy, either in place of, or in addition to bone marrow transplantation. Infusion of 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.

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, eight retrospective studies and one 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 Study (2006)	1995 - 2000[b]	2110	1.11 (0.86, 1.42)	1.10 (0.86, 1.39)	1.26 (0.95, 1.67)

[a] Analysis includes studies involving BM transplant during this period; some studies used GM-CSF
[b] Analysis includes patients receiving BM transplant during this period

Use of filgrastim for the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation
In normal donors, a 1 MU/kg/day (10 mcg/kg/day) dose administered subcutaneously for 4 - 5 consecutive days allows a collection of $\geq 4 \times 10^6$ $CD34^+$ cells/kg recipient body weight in the majority of the donors after two leukaphereses.

Use of filgrastim in patients, children or adults, with SCN (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in ANCs 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.

5.2 Pharmacokinetic properties

Randomised, double-blind, single and multiple dose, crossover studies in 204 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 mcg/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 median serum elimination half-life ($t_{1/2}$) of filgrastim after single subcutaneous doses ranged from 2.7 hours (1.0 MU/kg, 10 mcg/kg) to 5.7 hours (0.25 MU/kg, 2.5 mcg/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

Filgrastim was studied in repeated dose toxicity studies up to 1 year in duration which revealed changes attributable to the expected pharmacological actions including increases in leukocytes, myeloid hyperplasia in bone marrow, extramedullary granulopoiesis and splenic enlargement. These changes all reversed after discontinuation of treatment.

Effects of filgrastim on prenatal development have been studied in rats and rabbits. Intravenous (80 mcg/kg/day) administration of filgrastim to rabbits during the period of organogenesis was maternally toxic and increased spontaneous abortion, post-implantation loss, and decreased mean live litter size and foetal weight were observed.

Based on reported data for another filgrastim product similar to the reference filgrastim product, comparable findings plus increased foetal malformations were observed at 100 mcg/kg/day, a maternally toxic dose which corresponded to a systemic exposure of approximately 50 – 90 times the exposures observed in patients treated with the clinical dose of 5 mcg/kg/day. The no observed adverse effect level for embryo-foetal toxicity in this study was 10 mcg/kg/day, which corresponded to a systemic exposure of approximately 3 – 5 times the exposures observed in patients treated with the clinical dose.

In pregnant rats, no maternal or foetal toxicity was observed at doses up to 575 mcg/kg/day. Offspring of rats administered filgrastim during the peri-natal and lactation periods, exhibited a delay in external

differentiation and growth retardation (≥ 20 mcg/kg/day) and slightly reduced survival rate (100 mcg/kg/day).

Filgrastim had no observed effect on the fertility of male or female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glutamic acid
Sorbitol (E420)
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Zarzio must not be diluted with sodium chloride solution.

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

3 years.

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.

Within its shelf-life and for the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25 °C) for one single period of up to 8 days. At the end of this period, the product should not be put back in the refrigerator and should be disposed of.

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

6.5 Nature and contents of container

0.5 mL solution in a pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber), a stainless steel 29-gauge needle with an automatic needle guard and a needle cap (thermoplastic elastomer).

The pre-filled syringe bears printed markings from 0.1 mL to 1 mL, however, it is not designed to measure volumes less than 0.3 mL due to the spring mechanism.

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 filgrastim.

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 mcg/mL) is not recommended at any time.

For patients treated with filgrastim diluted to concentrations < 1.5 MU/mL (15 mcg/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 mcg) 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.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestr. 10
6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER(S)

Zarzio 30 MU/0.5 mL solution for injection or infusion in pre-filled syringe
EU/1/08/495/001
EU/1/08/495/002

EU/1/08/495/003
EU/1/08/495/004

Zarzio 48 MU/0.5 mL solution for injection or infusion in pre-filled syringe
EU/1/08/495/005
EU/1/08/495/006
EU/1/08/495/007
EU/1/08/495/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 February 2009
Date of latest renewal: 13 November 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Novartis Pharmaceutical Manufacturing GmbH
Biochemiestrasse 10
6250 Kundl
Austria

Name and address of the manufacturer(s) responsible for batch release

Sandoz GmbH
Biochemiestrasse 10
6336 Langkampfen
Austria

Novartis Pharmaceutical Manufacturing GmbH
Biochemiestrasse 10
6336 Langkampfen
Austria

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED SYRINGE WITH A NEEDLE SAFETY GUARD

1. NAME OF THE MEDICINAL PRODUCT

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

filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 30 million units (equivalent to 300 micrograms) filgrastim in 0.5 mL (60 MU/mL).

3. LIST OF EXCIPIENTS

Excipients: glutamic acid, polysorbate 80, sodium hydroxide, water for injections and sorbitol (E420).
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion in pre-filled syringe.

1 pre-filled syringe with a needle safety guard
3 pre-filled syringes with a needle safety guard
5 pre-filled syringes with a needle safety guard
10 pre-filled syringes with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only. Read the package leaflet before use.
Subcutaneous or intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestr. 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/495/001
EU/1/08/495/002
EU/1/08/495/003
EU/1/08/495/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zarzio 30 MU/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED SYRINGE WITH A NEEDLE SAFETY GUARD

1. NAME OF THE MEDICINAL PRODUCT

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

filgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 48 million units (equivalent to 480 micrograms) filgrastim in 0.5 mL (96 MU/mL).

3. LIST OF EXCIPIENTS

Excipients: glutamic acid, polysorbate 80, sodium hydroxide, water for injections and sorbitol (E420).
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion in pre-filled syringe.

1 pre-filled syringe with a needle safety guard
3 pre-filled syringes with a needle safety guard
5 pre-filled syringes with a needle safety guard
10 pre-filled syringes with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only. Read the package leaflet before use.
Subcutaneous or intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After dilution use within 24 hours.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestr. 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/495/005
EU/1/08/495/006
EU/1/08/495/007
EU/1/08/495/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zarzio 48 MU/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE WITH A NEEDLE SAFETY GUARD

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zarzio 30 MU/0.5 mL injection or infusion

filgrastim
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE WITH A NEEDLE SAFETY GUARD

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zarzio 48 MU/0.5 mL injection or infusion

filgrastim
SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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
filgrastim

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zarzio is and what it is used for

Zarzio is a white blood cell growth factor (granulocyte colony stimulating factor) and belongs to a group of proteins called cytokines. Growth factors are proteins that are produced naturally in the body but they can also be made using biotechnology for use as a medicine. Zarzio works by encouraging the bone marrow to produce more white blood cells.

A reduction in the number of white blood cells (neutropenia) can occur for several reasons and makes your body less able to fight infection. Zarzio stimulates the bone marrow to produce new white cells quickly.

Zarzio can be used:

- to increase the number of white blood cells after treatment with chemotherapy to help prevent infections;
- to increase the number of white blood cells after a bone marrow transplant to help prevent infections;
- before high-dose chemotherapy to make the bone marrow produce more stem cells which can be collected and given back to you after your treatment. These can be taken from you or from a donor. The stem cells will then go back into the bone marrow and produce blood cells;
- to increase the number of white blood cells if you suffer from severe chronic neutropenia to help prevent infections;
- in patients with advanced HIV infection which will help reduce the risk of infections.

2. What you need to know before you use Zarzio

Do not use Zarzio
- if you are allergic to filgrastim or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Zarzio.

Please tell your doctor before starting treatment **if you have**:
- osteoporosis (bone disease);
- sickle cell anaemia, as Zarzio may cause sickle cell crisis.

Please tell your doctor immediately during treatment with Zarzio, if you:
- get left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder [these may be symptoms of an enlarged spleen (splenomegaly), or possibly rupture of the spleen].
- notice unusual bleeding or bruising [these may be symptoms of a decrease in blood platelets (thrombocytopenia), with a reduced ability of your blood to clot].
- have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing as these could be signs of a severe allergic reaction (hypersensitivity).
- experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual (glomerulonephritis).
- have symptoms of inflammation of the aorta (the large blood vessel which transports blood from the heart to the body); this was reported in rare cases in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience these symptoms.

Loss of response to filgrastim

If you experience a loss of response or failure to maintain a response with filgrastim treatment, your doctor will investigate the reasons why including whether you have developed antibodies which neutralise filgrastim's activity.

Your doctor may want to monitor you closely, see section 4 of the package leaflet.

If you are a patient with severe chronic neutropenia, you may be at risk of developing cancer of the blood (leukaemia, myelodysplastic syndrome [MDS]). You should talk to your doctor about your risks of developing cancers of the blood and what testing should be done. If you develop or are likely to develop cancers of the blood, you should not use Zarzio unless instructed by your doctor.

If you are a stem cell donor, you must be aged between 16 and 60 years.

Take special care with other products that stimulate white blood cells.
Zarzio is one of a group of products that stimulate the production of white blood cells. Your healthcare professional should always record the exact product you are using.

Other medicines and Zarzio
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
Zarzio has not been tested in pregnant or breast-feeding women.
Zarzio is not recommended during pregnancy.

It is important to tell your doctor if you:
- are pregnant or breast-feeding;
- think you may be pregnant; or
- are planning to have a baby.

If you become pregnant during Zarzio treatment, please inform your doctor.

Unless your doctor directs you otherwise, you must stop breast feeding if you use Zarzio.

Driving and using machines
Zarzio may have a minor influence on your ability to drive and use machines. This medicine may cause dizziness. It is advisable to wait and see how you feel after taking Zarzio and before driving or operating machinery.

Zarzio contains sorbitol and sodium

Zarzio contains sorbitol (E420).

Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Zarzio

Always use this medicine exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.

How is Zarzio given and how much should I use?

Zarzio is usually given as a daily injection into the tissue just under the skin (known as a subcutaneous injection). It can also be given as a daily slow injection into the vein (known as an intravenous infusion). The usual dose varies depending on your illness and weight. Your doctor will tell you how much Zarzio you should take.

Patients having a bone marrow transplant after chemotherapy:
You will normally receive your first dose of Zarzio at least 24 hours after your chemotherapy and at least 24 hours after receiving your bone marrow transplant.

You, or people caring for you, can be taught how to give subcutaneous injections so that you can continue your treatment at home. However, you should not attempt this unless you have been properly trained first by your health care provider.

How long will I have to take Zarzio?

You will need to take Zarzio until your white blood cell count is normal. Regular blood tests will be taken to monitor the number of white blood cells in your body. Your doctor will tell you how long you will need to take Zarzio.

Use in children

Zarzio is used to treat children who are receiving chemotherapy or who suffer from severe low white blood cell count (neutropenia). The dosing in children receiving chemotherapy is the same as for adults.

Administration of small doses

You should not inject a dose of less than 0.3 mL with the pre-filled syringe, as it cannot be measured accurately because the 0.1 and 0.2 mL graduation marks are not visible.
If required, the solution for injection may be diluted.

If you use more Zarzio than you should

Do not increase the dose your doctor has given you. If you think you have injected more than you should, contact your doctor as soon as possible.

If you forget to use Zarzio

If you have missed an injection, or injected too little, contact your doctor as soon as possible. Do not take a double dose to make up for any missed doses.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor immediately during treatment**:**

- if you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), skin rash, itchy rash (urticaria), swelling of the face, lips, mouth, tongue or throat (angioedema) and shortness of breath (dyspnoea).
- if you experience a cough, fever and difficulty breathing (dyspnoea) as this can be a sign of Acute Respiratory Distress Syndrome (ARDS).
- if you get left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of your shoulder, as there may be a problem with your spleen [enlargement of the spleen (splenomegaly) or rupture of the spleen].
- if you are being treated for severe chronic neutropenia and you have blood in your urine (haematuria). Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine (proteinuria).
- if you have any of the following or combination of the following side effects:
  - swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion.

  These could be symptoms of a condition called “Capillary Leak Syndrome” which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.
- if you have a combination of any of the following symptoms:
  - fever, or shivering, or feeling very cold, high heart rate, confusion or disorientation, shortness of breath, extreme pain or discomfort and clammy or sweaty skin.

  These could be symptoms of a condition called “sepsis” (also called "blood poisoning"), a severe infection with whole-body inflammatory response which can be life threatening and needs urgent medical attention.
- if you experience kidney injury (glomerulonephritis). Kidney injury has been seen in patients who received filgrastim. Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual.

A common side effect of filgrastim use is pain in your muscles or bones (musculoskeletal pain), which can be helped by taking standard pain relief medicines (analgesics). In patients undergoing a stem cell or bone marrow transplant, Graft versus Host Disease (GvHD) may occur- this is a reaction of the donor cells against the patient receiving the transplant; signs and symptoms include rash on the palms of your hands or soles of your feet and ulcer and sores in your mouth, gut, liver, skin, or your eyes, lungs, vagina and joints. Very commonly seen in normal stem cell donors is increase in white blood cells (leukocytosis) and decrease of platelets which reduces the ability of blood to clot (thrombocytopenia), these will be monitored by your doctor.

Very common side effects (may affect more than 1 in 10 people)
- decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
- low red blood cell count (anaemia)
- headache
- diarrhoea
- vomiting
- nausea
- unusual hair loss or thinning (alopecia)
- tiredness (fatigue)
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus (mucosal inflammation)
- fever (pyrexia)

Common side effects (may affect up to 1 in 10 people)
- inflammation of the lung (bronchitis)
- upper respiratory tract infection
- urinary tract infection
- decreased appetite
- trouble sleeping (insomnia)
- dizziness
- decreased feeling of sensitivity, especially in the skin (hypoaesthesia)
- tingling or numbness of the hands or feet (paraesthesia)
- low blood pressure (hypotension)
- high blood pressure (hypertension)
- cough
- coughing up blood (haemoptysis)
- pain in your mouth and throat (oropharyngeal pain)
- nose bleeds (epistaxis)
- constipation
- oral pain
- enlargement of the liver (hepatomegaly)
- rash
- redness of the skin (erythema)
- muscle spasm
- pain when passing urine (dysuria)
- chest pain
- pain
- generalised weakness (asthenia)
- generally feeling unwell (malaise)
- swelling in the hands and feet (oedema peripheral)
- increase of certain enzymes in the blood
- changes in blood chemistry
- transfusion reaction

Uncommon side effects (may affect up to 1 in 100 people)
- increase in white blood cells (leukocytosis)
- allergic reaction (hypersensitivity)
- rejection of transplanted bone marrow (graft versus host disease)
- high uric acid levels in the blood, which may cause gout (hyperuricaemia) (Blood uric acid increased)
- liver damage caused by blocking of the small veins within the liver (veno-occlusive disease)
- lungs do not function as they should, causing breathlessness (respiratory failure)
- swelling and/or fluid in the lungs (pulmonary oedema)
- inflammation of the lungs (interstitial lung disease)

- abnormal x-rays of the lungs (lung infiltration)
- bleeding from the lung (pulmonary haemorrhage)
- lack of absorption of oxygen in the lung (hypoxia)
- bumpy skin rash (rash maculo-papular)
- disease which causes bones to become less dense, making them weaker, more brittle and likely to break (osteoporosis)
- injection site reaction

Rare side effects (may affect up to 1 in 1,000 people):
- severe pain in the bones, chest, gut or joints (sickle cell anaemia with crisis)
- sudden life-threatening allergic reaction (anaphylactic reaction)
- pain and swelling of the joints, similar to gout (pseudogout)
- a change in how your body regulates fluids within your body and may result in puffiness (fluid volume disturbances)
- inflammation of the blood vessels in the skin (cutaneous vasculitis)
- plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweets syndrome)
- worsening of rheumatoid arthritis
- unusual change in the urine
- bone density decreased
- inflammation of the aorta (the large blood vessel which transports blood from the heart to the body), see section 2
- formation of blood cells outside the bone marrow (extramedullary hematopoiesis)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zarzio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the syringe label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C).
Keep the pre-filled syringe in the outer carton in order to protect from light.
Accidental freezing will not harm Zarzio.

The syringe can be removed from the refrigerator and left at room temperature for a single period of maximum 8 days (but not above 25 °C). At the end of this period, the product should not be put back in the refrigerator and should be disposed of.

Do not use this medicine if you notice discolouration, cloudiness or particles, it should be a clear, colourless to slightly yellowish liquid.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zarzio contains

- The active substance is filgrastim.
  Zarzio 30 MU/0.5 mL solution for injection or infusion in pre-filled syringe: Each pre-filled syringe contains 30 MU filgrastim in 0.5 mL, corresponding to 60 MU/mL.
  Zarzio 48 MU/0.5 mL solution for injection or infusion in pre-filled syringe: Each pre-filled syringe contains 48 MU filgrastim in 0.5 mL, corresponding to 96 MU/mL.
- The other ingredients are glutamic acid, sorbitol (E420), polysorbate 80, sodium hydroxide and water for injections. See section 2 “Zarzio contains sorbitol and sodium”.

What Zarzio looks like and contents of the pack

Zarzio is a clear, colourless to slightly yellowish solution for injection or infusion in pre-filled syringe containing 0.5 mL solution.

Zarzio is available in packs containing 1, 3, 5 or 10 glass pre-filled syringes (type I glass) with a plunger stopper (bromobutyl rubber), a stainless steel 29-gauge needle with an automatic needle guard and a needle cap (thermoplastic elastomer).

The pre-filled syringe bears printed markings from 0.1 mL to 1 mL, however, it is not designed to measure volumes less than 0.3 mL due to the spring mechanism.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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6250 Kundl
Austria

Manufacturer

Sandoz GmbH
Biochemiestr. 10
6336 Langkampfen
Austria

Novartis Pharmaceutical Manufacturing GmbH
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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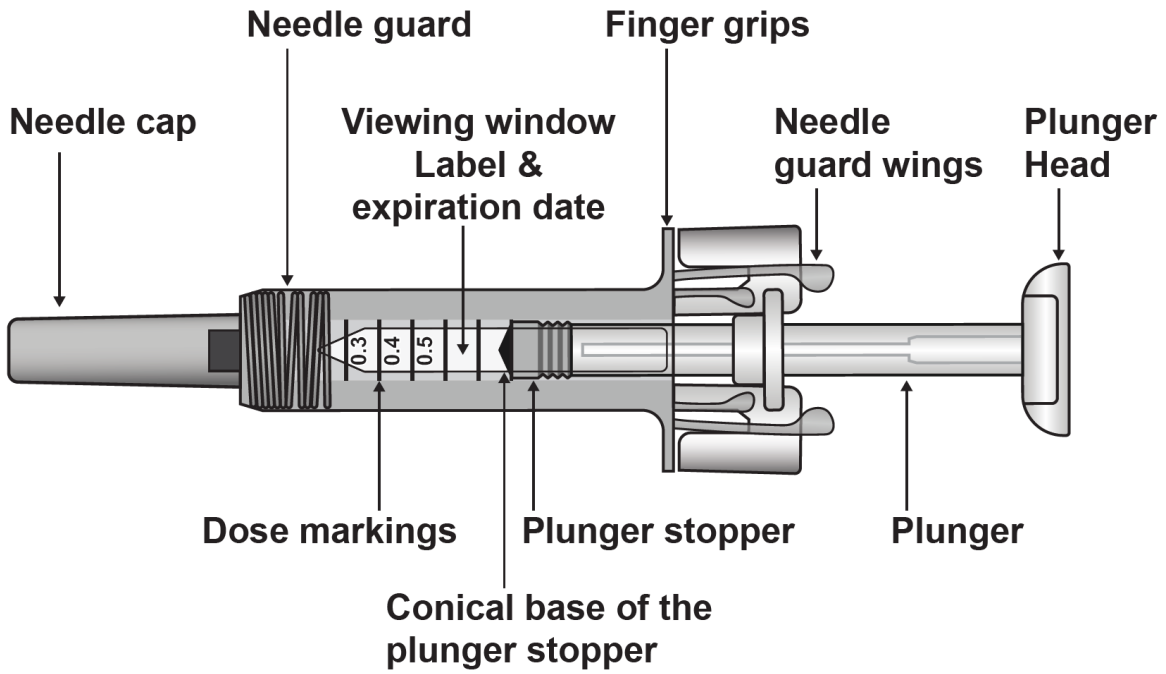
7. Instructions for use

To help avoid a possible infection, you should follow these instructions.

It is important not to try to inject yourself or someone else until you have been trained by your doctor, nurse or pharmacist. Please read all the instructions before injecting. Each sealed blister contains one pre-filled syringe.

Each pre-filled syringe contains 30 MU/0.5 mL or 48 MU/0.5 mL of filgrastim.

Figure 7-1 Zarzio pre-filled syringe with needle guard

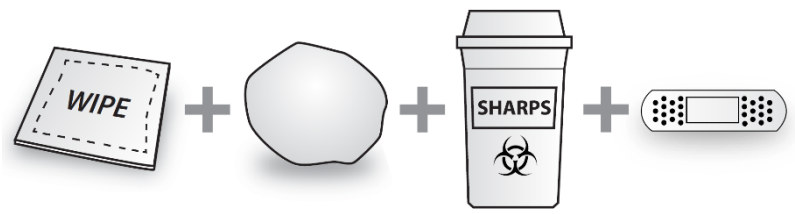


After the medication has been injected, the needle guard will be activated to cover the needle. The needle guard is intended to protect healthcare professionals, caregivers, and patients from accidental needle-stick injuries after the injection.

What you additionally need for your injection:

- 1 Alcohol swab
- 1 Cotton ball or gauze
- Sharps disposal container
- 1 Adhesive bandage

Figure 7-2 Additional items needed



Important safety information

Caution: Keep the pre-filled syringe out of the reach of children.

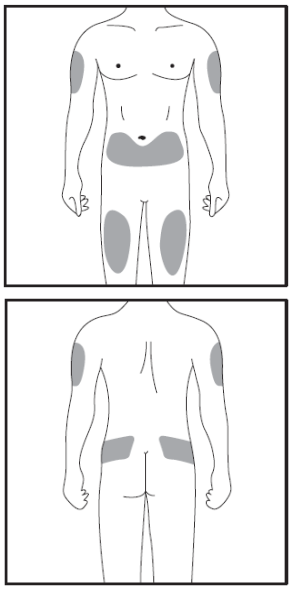
1. Do not open the outer box until you are ready to use the pre-filled syringe.
2. Do not use the pre-filled syringe if the seal of the blister is broken, as it may not be safe for you to use.
3. Do not use the pre-filled syringe if there is liquid in the plastic tray. Do not use the pre-filled syringe if the needle cap is missing or not securely attached. In all these instances, return the entire product pack to the pharmacy.
4. Do not attempt to inject a dose less than 0.3 mL from a pre-filled syringe. A dose less than 0.3 mL cannot be accurately measured using the Zarzio pre-filled syringe as the 0.1 and 0.2 mL graduation markings on the syringe barrel are not visible.
5. Never leave the pre-filled syringe unattended where others might tamper with it.
6. **Do not** shake the pre-filled syringe.
7. Be careful not to touch the needle guard wings before use. By touching them, the needle guard may be activated too early.
8. Do not remove the needle cap until just before you give the injection.
9. The pre-filled syringe cannot be re-used. Please dispose of the used pre-filled syringe immediately after use in a sharps container.
10. Do not use if the syringe has been dropped onto a hard surface or dropped after removing the needle cap.

Storage of the Zarzio pre-filled syringe

1. Store the pre-filled syringe in its outer carton box to protect it from light. Store it in a refrigerator between 2 °C and 8 °C (36 °F and 46 °F). **Do not** freeze.
2. Remember to take the blister out of the refrigerator and let it warm up for 15-30 minutes to allow it to reach room temperature before preparing it for the injection.
3. Do not use the pre-filled syringe after the expiration date shown on the outer box or syringe label. If it has expired, return the entire pack to the pharmacy.
4. The syringe can be removed from the refrigerator and left at room temperature for a single period of maximum 8 days (but not above 25 °C). At the end of this period, the product should not be put back in the refrigerator and should be disposed of.

The injection site

Figure 7-3 Injection sites



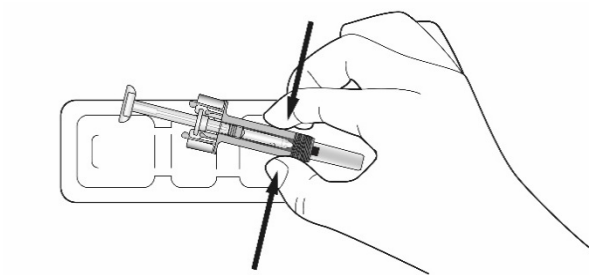
The injection site is the place on the body where you are going to use the pre-filled syringe.

- The recommended site is the front of your thighs. You may also use the lower abdomen, but **not** the area 5 cm (2 inches) around the navel (belly button).
- If a caregiver is giving you the injection, the outer upper arms and the upper areas of the buttocks may also be used.
- Choose a different site each time you give yourself an injection.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

Preparing the Zarzio pre-filled syringe ready for use

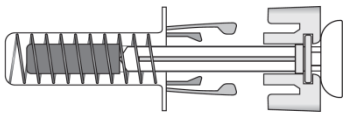
1. Take the blister containing the pre-filled syringe out of the refrigerator and leave it **unopened** for approximately 15-30 minutes, so that it can reach room temperature.
2. When you are ready to use the pre-filled syringe, open the blister and wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the pre-filled syringe from the blister by holding it in the middle as shown in Figure 7-4. Do not grab the plunger rod. Do not grab the needle cap.

Figure 7-4 Remove the pre-filled syringe from the blister



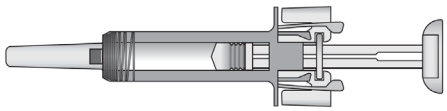
5. Check to ensure the plastic transparent needle guard is situated over the barrel of the glass syringe. If the transparent needle guard is covering the needle cap (as shown below Figure 7-5) the syringe has been activated, DO NOT use this syringe and take a new syringe. Figure 7-6 shows a ready to use syringe.

Figure 7-5 DO NOT USE



In this configuration the needle guard is ACTIVATED – DO NOT USE the pre-filled syringe

Figure 7-6 Ready to Use

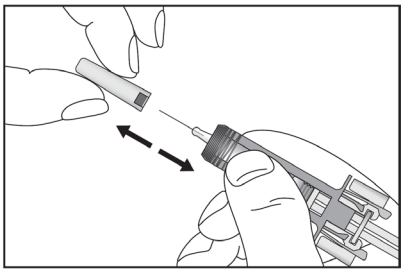


In this configuration the needle guard is NOT ACTIVATED and the pre-filled syringe is ready for use

6. Inspect the pre-filled syringe. The liquid should be clear. The color may be colorless to slightly yellowish, DO NOT USE if any other particulates and/or discolorations are observed and return the pre-filled syringe and the package it came in to the pharmacy.
7. DO NOT USE if the pre-filled syringe is broken or the needle guard activated. In all these instances, return the entire product pack to the pharmacy.

How to use the Zarzio pre-filled syringe

Figure 7-7 Remove needle cap



Carefully pull the needle cap straight off to remove it from the pre-filled syringe. Discard the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

Holding the syringe as shown, press slowly on the plunger to push out the excess medicine until the edge of the conical base of the plunger stopper lines up with the syringe marking for your prescribed dose. Below example for a dose of 0.4 mL.

Be careful not to touch the needle guard wings before use. The needle guard may be activated too early.

Check again to make sure the correct dose of Zarzio is in the pre-filled syringe.

Call your healthcare provider or nurse if you have problems measuring or injecting your dose of Zarzio.

Figure 7-8 Partial dose example for a dose of 0.4 mL

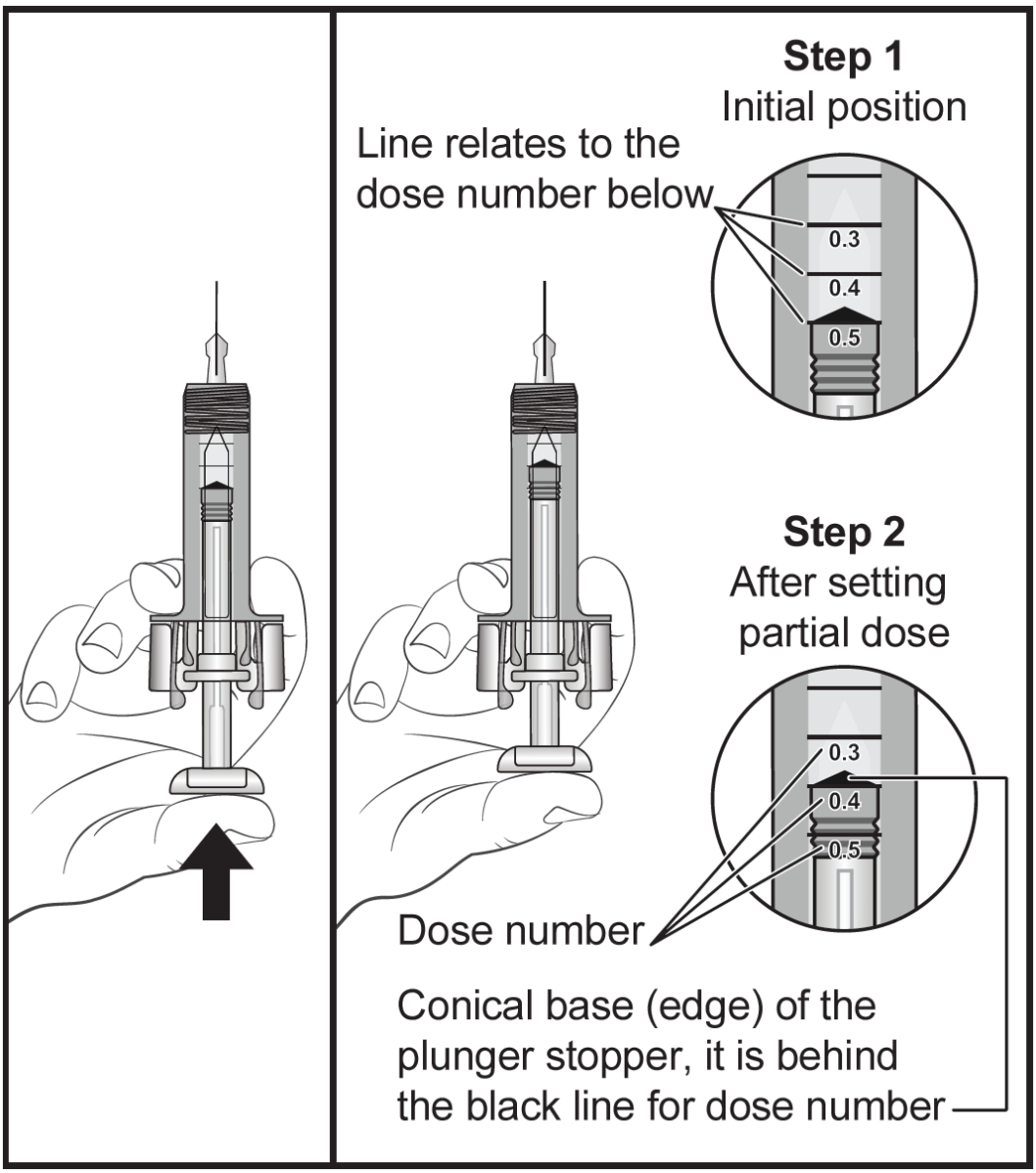
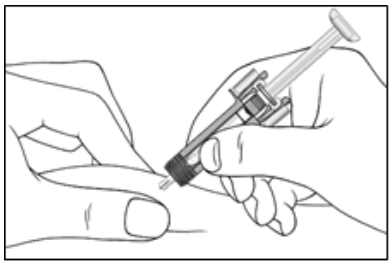
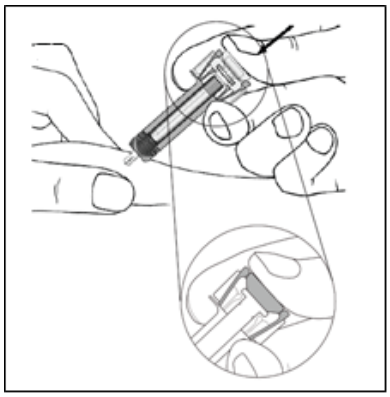


Figure 7-9 Insert needle



Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medication can be fully administered.

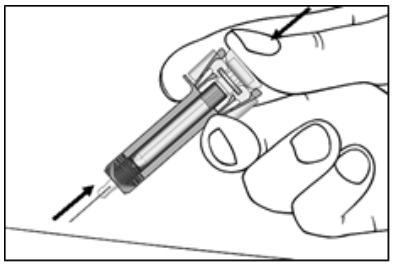
Figure 7-10 Depress plunger



Holding the pre-filled syringe as shown, **slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the needle guard wings.

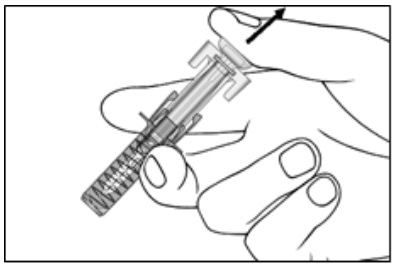
Keep the plunger pressed fully down while you hold the syringe in place for 5 seconds.

Figure 7-11 Withdraw needle



Keep the plunger fully depressed while you carefully pull the needle straight out from the injection site.

Figure 7-12 Release plunger

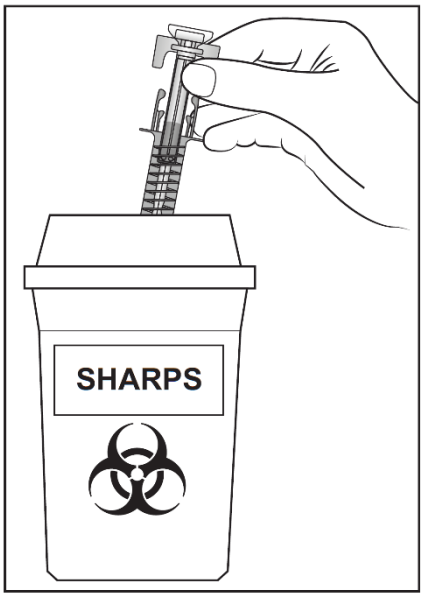


Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.

There may be a small amount of blood at the injection site. You can press a cotton ball or gauze onto the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Disposal instructions

Figure 7-13 Disposal



Dispose of the used syringe in a sharps container (closable, puncture-resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used.

The following information is intended for healthcare professionals only:

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. Zarzio must not be diluted with sodium chloride solutions.

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

For patients treated with filgrastim diluted to concentrations < 1.5 MU/mL (15 micrograms/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 micrograms) 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.

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.

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

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