PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORM:

Zarzio® 30 MU (Solution for injection or infusion)

Zarzio® 48 MU (Solution for injection or infusion)

COMPOSITION:

Active ingredient:

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

ZARZIO 30 MU: Each pre-filled syringe contains 30 million units (MU) / 300 µg filgrastim per 0,5 mL.

ZARZIO 48 MU: Each pre-filled syringe contains 48 million units (MU) / 480 µg filgrastim per 0,5 mL.

Inactive ingredients:

Glutamic acid, polysorbate 80, sorbitol and water for injection.

Contains sorbitol (25,00 mg per 0,5 mL syringe).

PHARMACOLOGICAL CLASSIFICATION:

A30.4 Biologicals - other

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. ZARZIO, which contains recombinant-metHuG-CSF, causes marked increases in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes.

Elevations of neutrophil count 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 to 2 days, and to normal levels within 1 to 7 days.

Absorption:

Filgrastim is detected in serum within 5 minutes after subcutaneous administration.

Distribution:

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

Following subcutaneous administration of recommended doses, serum concentrations were maintained above 10 ng/mL for 8 - 16 hours. The volume of distribution in blood is approximately 150 mL/kg.

Elimination:

The elimination of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous (SC) and intravenous (IV) administration. The serum elimination half-life of filgrastim is approximately 3,5 hours, with a clearance rate of approximately 0,6 mL/min/kg.

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.

INDICATIONS:

Established cytotoxic chemotherapy:

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia and its clinical sequelae in patients undergoing myeloablative therapy followed by bone marrow transplantation.

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

Severe chronic neutropenia (SCN):

In children and adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of ≤ 0,5 x 10^9/L, and a history of severe or recurrent infections, long term administration of ZARZIO is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Peripheral blood progenitor cell (PBPC) mobilisation:

The mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate haematopoietic recovery by infusion of such cells after myelosuppressive or myeloablative therapy.

The mobilisation of peripheral blood progenitor cells in normal donor (allogeneic) PBPC.

HIV infection:

Treatment of persistent neutropenia (ANC ≤ 1,0 x 10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other therapeutic options are inappropriate.

CONTRAINDICATIONS:

ZARZIO should not be administered to patients with known sensitivity to the active ingredient or to any of the excipients (see “COMPOSITION”).

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

ZARZIO use in the cancer setting in children.

Patients with severe renal and/ or hepatic impairment.

Pregnancy and lactation.

Normal donors < 16 years or > 60 years of age (see “WARNINGS AND SPECIAL PRECAUTIONS”).

Myelodysplastic syndromes.

Chronic myelogenous leukaemia.

WARNINGS AND SPECIAL PRECAUTIONS:

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, as in ZARZIO. Permanently discontinue ZARZIO in patients with clinically significant hypersensitivity. Do not administer ZARZIO to patients with a history of hypersensitivity to filgrastim, as in ZARZIO, or pegfilgrastim.

Immunogenicity:

There is a potential for immunogenicity. Rates of generation of antibodies against filgrastim, as in ZARZIO, are generally low. Binding antibodies may develop however; they have not been associated with neutralising activity.

Dilution:

ZARZIO should not be diluted with sodium chloride solutions (see “DOSAGE AND DIRECTIONS FOR USE, Incompatibilities”).

Malignant cell growth:

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

Myelodysplastic syndrome, or chronic myelogenous leukaemia:

The safety and efficacy of ZARZIO administration in patients with myelodysplastic syndrome, or chronic myelogenous leukaemia have not been established. Therefore, ZARZIO 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 Myeloid Leukaemia (AML), ZARZIO should be administered with caution. The safety and efficacy of ZARZIO 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.

Pulmonary adverse reactions:

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after granulocyte colony stimulating factor administration (see **"**SIDE EFFECTS"). 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 Acute Respiratory Distress Syndrome (ARDS). ZARZIO should be discontinued and appropriate treatment should be given.

Osteoporosis:

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

Capillary leak syndrome:

Capillary leak syndrome has been reported after granulocyte colony-stimulating factor administration, and is characterised by hypotension, hypoalbuminemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Glomerulonephritis:

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

Aortitis:

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 increase inflammatory markers (e.g., c-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF (see “SIDE EFFECTS).

Cancer patients:

Cases of splenomegaly and splenic rupture have been reported less frequently following administration of filgrastim, as in ZARZIO. Some cases of splenic rupture were fatal. Individuals receiving filgrastim, as in ZARZIO, who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Leukocytosis:

White blood cell counts of 100 x 10^9/L or greater have been observed in less than 5 % of patients receiving ZARZIO at doses above 0,3 MU/kg/day (3 µg/kg/day). No adverse 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 ZARZIO therapy. If leukocyte counts exceed 50 x 10^9/L after the expected nadir, ZARZIO should be discontinued immediately. However, during the period of administration of ZARZIO for peripheral blood progenitor cell mobilisation, it should be discontinued or its dose should be reduced if the leukocyte counts rise to > 70 x 10^9/L.

Risks associated with increased doses of chemotherapy:

Special caution should be used when treating patients with high dose chemotherapy because improved tumour outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic, and dermatologic effects (please refer to the prescribing information of the specific chemotherapy medicine used).

Effect of chemotherapy on erythrocytes and thrombocytes:

Treatment with ZARZIO 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 ZARZIO mobilised peripheral blood progenitor cells has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

The effects of ZARZIO in patients with substantially reduced myeloid progenitors have not been studied.
ZARZIO 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 granulocyte colony stimulating factor after allogeneic bone marrow transplantation (see “Pharmacodynamic Properties”).
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.
Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported in patients undergoing high dose chemotherapy followed by transplantation.

Severe chronic neutropenia patients (SCN):

Blood cell counts:

Thrombocytopenia has been reported commonly in patients receiving filgrastim, as in ZARZIO. Platelet counts should be monitored closely, especially during the first few weeks of ZARZIO therapy. Consideration should be given to intermittent cessation or decreasing the dose of ZARZIO 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 severe chronic neutropenias 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 severe chronic neutropenia treated with filgrastim as contained in ZARZIO. 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 ZARZIO 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 severe chronic neutropenia will predispose patients to cytogenetic abnormalities, MDS or leukemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

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

Splenic enlargement is a direct effect of treatment with ZARZIO. Thirty one percent (31 %) of patients in studies were documented as having palpable splenomegaly. Increases in volume, measured radiographically, occurred early during ZARZIO 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.

Patients undergoing Peripheral Blood Progenitor Cell (PCBC) Mobilisation:

There are no prospectively randomised comparisons of the two recommended mobilisation methods (ZARZIO 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 PBPC to achieve the recommended minimum yield (≥ 2,0 x 10^6 $CD34^+$ cells/kg) or acceleration of platelet recovery to the same degree.

Cytotoxic medicines exhibit particular toxicities to the haematopoietic progenitor pool and may adversely affect progenitor mobilisation.

Medicines 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 ZARZIO has been shown to be effective for progenitor mobilisation. When a peripheral blood progenitor cell transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitors mobilised in such patients before the administration of high-dose chemotherapy. If yields are inadequate, as measured by the criteria above, alternative forms of treatment not requiring progenitor support should be considered.

***Assessment of progenitor cell yields*:**

In assessing the number of progenitor cells harvested in patients treated with ZARZIO, 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 x 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 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 ZARZIO have not been assessed in normal donors < 16 years or > 60 years (see "CONTRAINDICATIONS").

Thrombocytopenia has been reported very frequently in patients receiving filgrastim as contained in ZARZIO. Platelet counts should therefore be monitored closely.

Transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim administration and leukapheresis was observed in 35 % of subjects studied.

Among these, two cases of platelets < 50 x 10^9/L were reported and attributed to the leukapheresis procedure. If more than one leukapheresis is required, particular attention should be paid to donors with platelets < 100 x 10^9/ L prior to leukapheresis; in general apheresis should not be performed if platelets < 75 x 10^9/L.

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

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

Donors who receive G-CSFs such as contained in ZARZIO for PBPC mobilisation should be monitored until haematological indices return to normal.

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

Nevertheless, a risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors 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, dyspnoea has been reported commonly and other pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltrates and hypoxia) have been reported uncommonly. In case of suspected or confirmed pulmonary adverse events, discontinuation of treatment with ZARZIO should be considered and appropriate medical care given.

Recipients of allogeneic peripheral blood progenitor cells mobilised with ZARZIO:

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

Patients with HIV infection:

Cases of splenomegaly have been reported frequently following administration of ZARZIO. Individuals receiving filgrastim as in ZARZIO, who report left upper abdominal and/or shoulder tip pain should therefore be evaluated for an enlarged spleen or splenic rupture.

***Blood cell counts*:**

Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of ZARZIO therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of ZARZIO. It is recommended that the ANC is measured daily for the first 2 - 3 days of ZARZIO 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 ZARZIO.

Risk associated with increased doses of myelosuppressive medicinal products:

Treatment with ZARZIO 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 ZARZIO 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 ZARZIO for treatment of neutropenia. The effects of ZARZIO on neutropenia due to bone marrow infiltrating infection or malignancy have not been well established.

***Sickle cell trait and sickle cell disease*:**

Sickle cells crises, in some cases fatal, have been reported with the use of ZARZIO in subjects with sickle cell trait or sickle cell disease. Medical practitioners should exercise caution when prescribing ZARZIO in patients with sickle cell trait or sickle cell disease.

All patients:

ZARZIO contains sorbitol (25 mg per 0,5 mL syringe) and may have a laxative effect. Patients with the rare hereditary problems of sorbitol intolerance should not be given ZARZIO (see “COMPOSITION”).

ZARZIO contains less than 1 mmol (23 mg) sodium per 0,3 mg/mL, i.e., essentially sodium-free.

In order to improve the traceability of granulocyte-colony stimulating factors (G-CSF’s), the trade name of the administered products should be clearly recorded in the patient file.

Effects on ability to drive and use machines:

ZARZIO may have a minor influence on the ability to drive and use machines. Dizziness may occur following the administration of ZARZIO (see “SIDE EFFECTS”).

INTERACTIONS:

The safety and efficacy of ZARZIO 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 ZARZIO 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 as contained in ZARZIO 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. Lithium promotes the release of neutrophils, and it is likely to potentiate the effect of ZARZIO. This interaction has not been formally investigated.

PREGNANCY AND LACTATION:

ZARZIO is not recommended during pregnancy (see “CONTRAINDICATIONS”).

There are no or limited amount of data from the use of filgrastim as in ZARZIO, 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. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated.

ZARZIO is contraindicated in pregnancy and lactation (see “CONTRAINDICATIONS”).

Breastfeeding:

Mothers on treatment with ZARZIO should not breastfeed their babies.

It is unknown whether filgrastim as in ZARZIO or any of its metabolites are excreted in breast milk. A risk to the newborns/infants cannot be excluded.

Fertility:

Filgrastim, as in ZARZIO, did not affect reproductive performance or fertility in male or female rats.

DOSAGE AND DIRECTIONS FOR USE:

Established cytotoxic chemotherapy:

The recommended dose of ZARZIO is 0,5 MU (5 µg)/kg/day. The first dose of ZARZIO should not be administered less than 24 hours following cytotoxic chemotherapy.

ZARZIO may be given as a daily subcutaneous injection, or as a daily intravenous infusion diluted in 5 % glucose solution, given over 30 minutes (refer to “Instructions on dilutions”). Subcutaneous administration is the preferred route of administration.

There is some evidence that administration of a single intravenous dose 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 trials, a subcutaneous dose of 230 µg/m^2/day (4,0 to 8,4 µg/kg/day) was used.

Daily dosing with ZARZIO should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range.

Following established chemotherapy for solid tumours, lymphomas, and lymphoid 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 (AML) 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 ZARZIO therapy. However, for a sustained therapeutic response, ZARZIO therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of ZARZIO therapy, prior to the time of the expected neutrophil nadir, is not recommended.

In patients treated with myeloablative therapy followed by bone marrow transplantation (BMT):

The recommended starting dose of ZARZIO is 1,0 MU (10 µg)/kg/day, given as a 30 minute or 24 hour intravenous infusion or 1,0 MU (10 µg)/kg/day, given by continuous 24 hour subcutaneous infusion.

ZARZIO should be diluted in 20 mL of 5 % glucose solution.

The first dose of ZARZIO 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 ZARZIO should be titrated against the neutrophil response as follows:

Absolute neutrophil count (ANC)	***ZARZIO dose adjustment***
ANC > 1,0 x 10^9 / L for 3 consecutive days	Reduce to 0,5 MU/kg/day
Then, if ANC remains, 1,0 x 10^9 / L for 3 more consecutive days	Discontinue ZARZIO
If the ANC decreases to < 1,0 x 10^9 / L during the treatment period, the dose of ZARZIO should be re-escalated according to the above steps.	

Mobilisation of Peripheral Blood Progenitor Cells (PBPC) in patients undergoing myelosuppressive or myeloablative therapy followed by autologous peripheral blood progenitor cell transplantation:
The recommended dose of ZARZIO for PBPC mobilisation when used alone is 1,0 MU (10 µg)/kg/day), as a 24 hour subcutaneous injection or a single daily subcutaneous injection for 5 - 7 consecutive days. For infusions, ZARZIO should be diluted in 20 mL of 5 % glucose solution (refer to instructions on dilutions). Timing of leukapheresis: 1 or 2 leukaphereses on days 5 and 6 are often sufficient. In other circumstances, additional leukaphereses may be necessary. ZARZIO dosing should be maintained until the last leukapheresis.

The recommended dose of ZARZIO for PBPC mobilisation after myelosuppressive chemotherapy is 0,5 MU (5 µg)/kg/day given daily by subcutaneous injection from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from < 0,5 x 10^9/L to > 5,0 x 10^9/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukaphereses are recommended.

For the Mobilisation of Peripheral Blood Progenitor Cells (PBPC) in normal donors prior to allogeneic PBPC transplantation:
For PBPC mobilisation in normal donors prior to allogeneic PBPC transplantation, ZARZIO should be

administered at 10 µg/kg/day, subcutaneously for 4 - 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4 x 10^6 $CD34^+$ cells/kg recipient bodyweight (BW).

In patients with severe chronic neutropenia (SCN)

***Congenital neutropenia*:**

The recommended starting dose is 1,2 MU (12 µg)/kg/day subcutaneously as a single dose or in divided doses.

***Idiopathic or cyclic neutropenia*:**

The recommended starting dose is 0,5 MU (5 µg)/kg/day subcutaneously as a single dose or in divided doses.

***Dose adjustments*:**

ZARZIO should be administered daily, by subcutaneous injection, until the neutrophil count has reached and can be maintained at more than 1,5 x 10^9/L.
When the response has been obtained, the minimal effective dose to maintain this level should be established. Long-term daily administration is required to maintain an adequate neutrophil count.

After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently the dose may be individually adjusted every 1 - 2 weeks to maintain the average neutrophil count between 1,5 x 10^9/L and 10 x 10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97 % of patients who responded had a complete response at doses ≤ 24 µg/kg/day. The long-term safety of ZARZIO administration above 24 µg/kg/day in patients with severe chronic neutropenia (SCN) has not been established.

ZARZIO therapy should only be given in collaboration with an oncology centre, which has experience in granulocyte colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities.

The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology

centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.
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 dosage requirements for these patients cannot be made.

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

Paediatric use in severe chronic neutropenia (SCN) and cancer setting
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.
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.

In patients with HIV infection:

***Reversal of neutropenia*:**
The recommended starting dose of ZARZIO is 0,1 MU (1 µg)/kg/day given daily by subcutaneous injection with titration up to a maximum of 0,4 MU (4 µg)/kg/day) until a normal neutrophil count is reached and can be maintained (ANC > 2,0 x 10^9/L).

In clinical studies, > 90 % of patients responded at these doses, achieving reversal of neutropenia in a median of 2 days. In a small number of patients (< 10 %), doses up to 1,0 MU (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 (300 µg/day) by subcutaneous injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2,0 x 10^9/L.

In clinical studies, dosing with 30 MU/day (300 µg/day) on 1 to 7 days per week was required to maintain the ANC > 2,0 x 10^9/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC > 2,0 x 10^9/L.

Instructions on dilutions:

If required, ZARZIO may be diluted in 5 % glucose. Dilution to a final concentration less than 0,2 MU (2 µg) per mL is not recommended at any time. The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

For patients treated with filgrastim diluted to concentrations below 1,5 MU (15 µg) per mL, human serum albumin (HSA) should be added to a final concentration of 2 mg/mL.

Example: In a final injection volume of 20 mL, total doses of filgrastim less than 30 MU (300 µg) should be given with 0,2 mL of 20 % human albumin Ph. Eur. added.

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

Incompatibilities:

ZARZIO should not be diluted with sodium chloride solutions.

Diluted ZARZIO may be adsorbed to glass and plastic materials.

ZARZIO must not be mixed with other products except those mentioned in “Instructions on dilutions”.

SIDE EFFECTS:

a) Summary of safety profile:

The most serious side effects that may occur during ZARZIO 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 SVN 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 to moderate in 10 %, and severe in 3 % of patients.

b) Tabulated summary of adverse reactions:

The data in the below table describe adverse reactions reported from clinical trials and spontaneous reporting.

System Order Class	Frequent	Less Frequent
Infections and infestations:	Sepsis Bronchitis Upper respiratory tract infection Urinary tract infection	
Blood and lymphatic system disorders:	Thrombocytopenia Anaemia Splenomegaly[a] Haemoglobin decreased[e]	Leukocytosis[a] Splenic rupture[a] Sickle cell anaemia with crisis
Immune system disorder:		Hypersensitivity Medicines Hypersensitivity 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 pyrophosphate) Fluid volume disturbances
Psychiatric disorders:	Insomnia	
Nervous system disorders:	Headache[a]	

	Dizziness Hypoaesthesia Paraesthesia	
Vascular disorder:	Hypertension Hypotension	Veno-occlusive disease[d] Capillary leak syndrome[a] Aortitis
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 disorder:	Hepatomegaly Blood alkaline phosphatase increased	Aspartate aminotransferase increased Gamma-glutamyl transferase increased
Skin and subcutaneous tissue disorders:	Alopecia[a] Rash[a] Erythema	Rash maculopapular 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 administrative site conditions:	Fatigue[a] Mucosal inflammation[a] Pyrexia Chest pain[a]	Injection site reaction

	Pain[a] Asthenia[a] Malaise[e] Oedema peripheral[e]	
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 "Description of selected adverse reactions")

[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 “WARNINGS AND SPECIAL PRECAUTIONS”).

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 “WARNINGS AND SPECIAL PRECAUTIONS”).

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 “WARNINGS AND SPECIAL PRECAUTIONS”).

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 x 10^9/L) was observed in 41 % of normal donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35 % of donors (see “WARNINGS AND SPECIAL PRECAUTIONS”).

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 “WARNINGS AND SPECIAL PRECAUTIONS”).

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.

f) Post Marketing Adverse Events

The following side effects have been reported with post marketing use of filgrastim.

System Organ Class	**Adverse reaction**
Blood and lymphatic disorders:	Sickle cell crisis

	Splenic rupture
Immune system disorders:	Allergic-type reactions, including anaphylaxis, skin rash and urticaria
Metabolism and nutrition disorders:	Increase in uric acid, alkaline phosphatase and lactate dehydrogenase
Skin and subcutaneous tissue disorders:	Sweet's syndrome (acute febrile dermatosis)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The effects of ZARZIO overdose have not been established. However, side effects may be precipitated and be of increased severity. Discontinuation of ZARZIO therapy usually results in a 50 % decrease in circulating neutrophils within 1 – 2 days, with a return to normal level in 1 – 7 days. Treatment is symptomatic and supportive.

IDENTIFICATION:

ZARZIO 30 MU: 1 mL long clear glass syringe with a grey stopper and stacked needle containing a colourless to slightly yellowish solution. Free from visible particulate matter.

ZARZIO 48 MU: 1 mL long clear glass syringe with a grey stopper and stacked needle containing a colourless to slightly yellowish solution. Free from visible particulate matter.

PRESENTATIONS:

Primary packaging: Pre-filled colourless, transparent, 1 mL glass syringe containing 0,5 mL solution, with stainless steel injection needle, protected by a grey rubber formulation needle shield (guard) and with a grey flurotec coated bromobutyl plunger stopper.

Secondary packaging: Rigid polypropylene needle shield (cap) and polypropylene or polycarbonate plunger rod.

Pack sizes of 1, 3, 5 or 10 pre-filled syringes packed in a carton.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS:

Store between 2 – 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 (at or below 25 °C) for one single period of up to 72 hours. At the end of this period, the product should not be put back in the refrigerator and should be disposed of.

Diluted ZARZIO solutions should not be prepared more than 24 hours before administration and should be stored between 2 – 8 °C.

Accidental exposure to freezing temperatures does not adversely affect the stability of ZARZIO.

ZARZIO syringes are for single use only.

Any unused portion of ZARZIO should be discarded in accordance with local requirements

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

ZARZIO 30 MU: 47/30.4/0603

ZARZIO 48 MU: 47/30.4/0604

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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[1] Company Reg. No.: 1990/001979/07