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DH Circular No /2007

Attention all Consultants
Medical Officers
Pharmacists
Nurses

Re: Filgrastim temporary change in Formulation

Kindly note that a different preparation of Filgrastim [recombinant human granulocyte-colony stimulating factor (G-CSF)] is being procured temporarily.

Filgrastim previously available as a single-use vial of 30 million units [MU/MIU] (300 micrograms (mcg)) in an injectable solution of 1mL [Neutromax®] will be temporary replaced by a single-use pre-filled syringe of 30 MU (300mcg) in an injectable solution of 0.5mL [Neupogen® Singlejet].

Please note that the presently available formulation of filgrastim [Neupogen® Singlejet] has the same amount of filgrastim per vial/pre-filled syringe [30 MU (300mcg)] as the previously available formulation [Neutromax®] BUT in half the volume (i.e. in 0.5mL instead of the previous 1mL). Therefore, **the present formulation is twice as concentrated as the previous one**.

The Summary of Product Characteristics of Filgrastim 30 MU in 0.5mL is annexed for your reference and information.

For your attention please,

Dr. R. Busuttil
Director General (Health)

Annex 1

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Neupogen Singleject 30MU and 48MU

1. NAME OF THE MEDICINAL PRODUCT

NEUPOGEN Singleject 30 MU (0.6 mg/ml)

Solution for injection in a pre-filled syringe

NEUPOGEN Singleject 48 MU (0.96 mg/ml)

Solution for injection in a pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 30 million units (300 micrograms (μg)) of filgrastim in 0.5 ml (0.6 mg/ml).

Each pre-filled syringe contains 48 million units (480 micrograms (μg)) of filgrastim in 0.5 ml (0.96 mg/ml).

Filgrastim (recombinant methionyl human granulocyte-colony stimulating factor) is produced by r-DNA technology in E. coli (K12).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.

Concentrate for solution for infusion in a pre-filled syringe.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEUPOGEN is indicated for the 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 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 NEUPOGEN are similar in adults and children receiving cytotoxic chemotherapy.

NEUPOGEN is indicated for the mobilisation of peripheral blood progenitor cells (PBPC).

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

NEUPOGEN is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0 x10^9/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

Established cytotoxic chemotherapy

The recommended dose of NEUPOGEN is 0.5 MU (5 μg)/kg/day. The first dose of NEUPOGEN should not be administered less than 24 hours following cytotoxic chemotherapy. NEUPOGEN may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minutes (see below, section 6.6 'Instructions for use and handling' for instructions on dilutions). The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance. In randomised clinical trials, a subcutaneous dose of 230 μg/m^2/day (4.0 to 8.4 μg/kg/day) was used.

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

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

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of NEUPOGEN 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. NEUPOGEN should be diluted in 20 ml of 5% glucose solution (see section 6.6 'Instructions for use and handling' for instructions on dilutions).

The first dose of NEUPOGEN should not be administered less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow infusion.

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

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

For the 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 NEUPOGEN for PBPC mobilisation when used alone is 1.0 MU (10 μg)/kg/day as a 24 hour subcutaneous continuous infusion or a single daily subcutaneous injection for 5 to 7 consecutive days. For infusions NEUPOGEN should be diluted in 20 ml of 5% glucose solution (see section 6.6 'Instructions for use and handling' for instructions on dilutions). Timing of leukapheresis: one or two leukaphereses on days 5 and 6 are often sufficient. In other circumstances, additional leukaphereses may be necessary. NEUPOGEN dosing should be maintained until the last leukapheresis.

The recommended dose of NEUPOGEN 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 < 0.5×10^9/L to > 5.0×10^9/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 (PBPCs) in normal donors prior to allogeneic peripheral blood progenitor cell transplantation

For PBPC mobilisation in normal donors, NEUPOGEN should be administered at 10 μg/kg/day subcutaneously for 4 to 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4×10^6 $CD34^+$ cells/kg recipient bodyweight.

In patients with severe chronic neutropenia

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 adjustment: NEUPOGEN 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 to 2 weeks to maintain the average neutrophil count between 1.5 x 10^9/L and 10 x 10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97% of patients who responded had a complete response at doses □ 24 μg/kg/day. The long-term safety of NEUPOGEN administration above 24 μg/kg/day in patients with severe chronic neutropenia has not been established.

Other particulars

NEUPOGEN 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.

Clinical trials with NEUPOGEN 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.

Studies of NEUPOGEN 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 severe chronic neutropenia (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 severe chronic neutropenia.

Data from clinical studies in paediatric patients indicate that the safety and efficacy of NEUPOGEN 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

For reversal of neutropenia

The recommended starting dose of NEUPOGEN 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 x10^9/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.

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 (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 (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.

4.3 Contraindications

NEUPOGEN should not be administered to patients with known hypersensitivity to filgrastim or to any of the excipients. NEUPOGEN should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

NEUPOGEN should not be administered to patients with severe congenital neutropenia (Kostman's syndrome) with abnormal cytogenetics (see also Section 4.4, Special warnings and precautions for use).

4.4 Special warnings and precautions for use

Malignant cell growth

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

The safety and efficacy of NEUPOGEN administration in patients with myelodysplastic syndrome, or chronic myelogenous leukaemia have not been established.

NEUPOGEN is not indicated for use in these conditions. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

In view of limited safety and efficacy data in patients with secondary AML, NEUPOGEN should be administered with caution.

The safety and efficacy of NEUPOGEN 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.

Other special precautions

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

Rare (> 0.01% and <0.1%) pulmonary adverse effects, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of

pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS). NEUPOGEN should be discontinued and appropriate treatment given.

The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Special precautions in cancer patients

Leucocytosis

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

Risks associated with increased doses of chemotherapy

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

Treatment with NEUPOGEN 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 NEUPOGEN-mobilised PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Other special precautions

The effects of NEUPOGEN in patients with substantially reduced myeloid progenitors have not been studied. NEUPOGEN 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).

The effect of NEUPOGEN on graft versus host disease has not been defined.

Known cases of Hereditary Fructose Intolerance. NEUPOGEN contains sorbitol as an excipient at a concentration of 50 mg/ml. It is unlikely that as a consequence of treatment with NEUPOGEN alone that sufficient sorbitol will be infused to result in clinically relevant

toxicity in affected individuals. However, in cases of HFI caution is advised.

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

Special precautions in patients undergoing peripheral blood progenitor cell mobilisation

Mobilisation

There are no prospectively randomised comparisons of the two recommended mobilisation methods (NEUPOGEN 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 x 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 NEUPOGEN, 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 NEUPOGEN, 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 x 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 peripheral blood progenitor cell mobilisation

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

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

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

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

NEUPOGEN administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 70 x10^9/L.

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

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

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 granulocyte-colony stimulating factors (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.

Special precautions in recipients of allogeneic peripheral blood progenitor cells mobilised with NEUPOGEN

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

Special precautions in severe chronic neutropenia (SCN) patients

Blood cell counts

Platelet counts should be monitored closely, especially during the first few weeks of NEUPOGEN therapy. Consideration should be given to intermittent cessation or decreasing the dose of NEUPOGEN 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 NEUPOGEN. 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 NEUPOGEN therapy. A subset of approximately 12% of patients who had normal cytogenetic evaluations at baseline were subsequently found to have abnormalities, including monosomy 7, on routine repeat evaluation. If patients with severe chronic neutropenia develop abnormal cytogenetics, the risks and benefits of continuing NEUPOGEN should be carefully weighed; NEUPOGEN should be discontinued if MDS or leukaemia occur. It is currently unclear whether long-term treatment of patients with severe chronic neutropenia will predispose patients to cytogenetic abnormalities, MDS or leukaemic transformation. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months).

Other special precautions

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

Splenic enlargement is a direct effect of treatment with NEUPOGEN. Thirty-one percent (31%) of patients in studies were documented as having palpable splenomegaly. Increases in volume, measured radiographically, occurred early during NEUPOGEN 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 urinanalysis should be performed to monitor this event.

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

Special precautions in patients with HIV infection

Blood cell counts

Absolute neutrophil count (ANC) should be monitored closely, especially during the first few weeks of NEUPOGEN therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial dose of NEUPOGEN. It is recommended that the ANC is measured daily for the first 2 to 3 days of NEUPOGEN administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first two weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 30 MU (300 μg)/day of NEUPOGEN, 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 NEUPOGEN.

Risk associated with increased doses of myelosuppressive medications

Treatment with NEUPOGEN alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medications. As a result of the potential to receive higher doses or a greater number of these medications with NEUPOGEN 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 NEUPOGEN for treatment of neutropenia. The effects of NEUPOGEN on neutropenia due to bone marrow infiltrating infection or malignancy have not been well established.

Special precautions in sickle cell disease

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

4.5 Interaction with other medicinal products and other forms of interaction

The safety and efficacy of NEUPOGEN 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 NEUPOGEN 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 NEUPOGEN 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 NEUPOGEN. Although this interaction has not been formally investigated, there is no evidence that such an interaction is harmful.

4.6 Pregnancy and lactation

The safety of NEUPOGEN has not been established in pregnant women. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. There is no evidence from studies in rats and rabbits that NEUPOGEN is teratogenic. An increased incidence of embryo-loss has been observed in rabbits, but no malformation has been seen. In pregnancy, the possible risk of NEUPOGEN use to the foetus must be weighed against the expected therapeutic benefit.

It is not known whether NEUPOGEN is excreted in human milk. NEUPOGEN is not recommended for use in nursing women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In cancer patients

In clinical trials, the most frequent undesirable effects attributable to NEUPOGEN at the recommended dose were mild or moderate musculoskeletal pain, occurring in 10%, and severe musculoskeletal pain in 3% of patients. Musculoskeletal pain is usually controlled with standard analgesics. Less frequent undesirable effects include urinary abnormalities predominantly mild or moderate dysuria.

In randomised, placebo-controlled clinical trials, NEUPOGEN did not increase the incidence of undesirable effects associated with cytotoxic chemotherapy. Undesirable effects reported with equal frequency in patients treated with NEUPOGEN/ chemotherapy and placebo/chemotherapy included nausea and vomiting, alopecia, diarrhoea, fatigue, anorexia, mucositis, headache, cough, skin rash, chest pain, generalised weakness, sore throat, constipation and unspecified pain.

Reversible, dose-dependent and usually mild or moderate elevations of lactate dehydrogenase, alkaline phosphatase, serum uric acid, and gamma-glutamyl transpeptidase occurred with NEUPOGEN in approximately 50%, 35%, 25%, and 10% of patients, respectively at recommended doses.

Transient decreases in blood pressure, not requiring clinical treatment, have been reported occasionally.

Vascular disorders, including veno-occlusive disease and fluid volume disturbances, have been reported occasionally in patients undergoing high dose chemotherapy followed by autologous bone marrow transplantation. The causal association with NEUPOGEN has not been established.

Very rare events of cutaneous vasculitis have been reported in patients treated with NEUPOGEN. The mechanism of vasculitis in patients receiving NEUPOGEN is unknown.

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

Exacerbation of rheumatoid arthritis has been observed in individual cases.

Rare pulmonary adverse effects including interstitial pneumonia, pulmonary oedema, and pulmonary infiltrates have been reported in some cases with an outcome of respiratory failure or adult respiratory distress syndrome (ARDS), which may be fatal (see 4.4).

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

Isolated cases of sickle cells crises have been reported in patients with sickle cell disease (see 4.4).

Frequency	**Body System**	**Undesirable Effect**
Very Common (> 10%)	Gastrointestinal	Nausea/Vomiting
	Liver	Elevated GGT
	Metabolic/Nutrition	Elevated Alkaline Phosphatase
		Elevated LDH
		Elevated Uric Acid
Common (1 – 10%)	Body General	Fatigue
		Generalised Weakness
	CNS/PNS	Headache
	Gastrointestinal	Constipation
		Anorexia
		Diarrhoea
		Muscositis
	Musculoskeletal	Chest Pain
		Musculoskeletal Pain
	Respiratory	Cough
		Sore Throat
	Skin	Alopecia
		Skin Rash
Uncommon (< 1%)	Body General	Unspecified Pain
Rare (< 0.1%)	Vascular	Vascular Disorder
Very Rare (< 0.01%)	Body General	Allergic Reaction
	Musculoskeletal	Rheumatoid Arthritis
		Exacerbation
	Respiratory	Pulmonary Infiltrates
	Skin	Sweet's Syndrome
		Cutaneous Vasculitis
	Urinary	Urinary Abnormalities

In peripheral blood progenitor cell mobilisation in normal donors

The most commonly reported undesirable effect was mild to moderate transient musculo-

skeletal pain. Leukocytosis (WBC > 50 x 10^9/L) was observed in 41% of donors and transient thrombocytopenia (platelets < 100 x 10^9/L) following filgrastim and leukapheresis was observed in 35% of donors.

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

Exacerbation of arthritic symptoms has been observed very rarely.

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

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

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 granulocyte-colony stimulating factors (G-CSFs) (see Section 4.4).

Frequency	**Body System**	**Undesirable Effect**
Very Common (> 10%)	CNS/PNS	Headache
	Haematological	Leucocytosis
		Thrombocytopenia
	Musculoskeletal	Musculoskeletal Pain
Common (1 – 10%)	Metabolic/Nutrition	Elevated Alkaline Phosphatase
		Elevated LDH
Uncommon (< 1%)	Body General	Severe Allergic Reaction
	Haematological	Spleen Disorder
	Metabolic/Nutrition	SGOT Increased
		Hyperuricaemia
	Musculoskeletal	Rheumatoid Arthritis
		Exacerbation

In severe chronic neutropenia (SCN) patients

Undesirable effects related to NEUPOGEN therapy in SCN patients have been reported and for some their frequency tend to decrease with time.

The most frequent undesirable effects attributable to NEUPOGEN were bone pain, and general musculoskeletal pain.

Other undesirable effects seen include splenic enlargement, which may be progressive in a minority of cases and thrombocytopenia. Headache and diarrhoea have been reported shortly after starting NEUPOGEN therapy, typically in less than 10% of patients. Anaemia and epistaxis have also been reported.

Transient increases with no clinical symptoms were observed in serum uric acid, lactic dehydrogenase, and alkaline phosphatase. Transient, moderate decreases in non-fasting blood glucose have also been seen.

Undesirable effects possibly related to NEUPOGEN therapy and typically occurring in < 2% of SCN patients were injection site reaction, headache, hepatomegaly, arthralgia, alopecia, osteoporosis, and rash.

During long term use cutaneous vasculitis has been reported in 2% of SCN patients. There have been very few instances of proteinuria/haematuria.

Frequency	**Body System**	**Undesirable Effect**
Very Common (> 10%)	Haematological	Anaemia
		Splenomegaly
	Metabolic/Nutrition	Decreased Glucose
		Elevated Alkaline Phosphatase
		Elevated LDH
		Hyperuricaemia
	Musculoskeletal	Musculoskeletal Pain
	Respiratory	Epistaxis
Common (1 – 10%)	CNS/PNS	Headache
	Gastrointestinal	Diarrhoea
	Haematological	Thrombocytopenia
	Liver	Hepatomegaly
	Musculoskeletal	Osteoporosis
	Skin	Alopecia
		Cutaneous Vasculitis
		Injection Site Pain
		Rash
Uncommon (< 1%)	Haematological	Spleen Disorder
	Urinary	Haematuria
		Proteinuria

In patients with HIV

In clinical studies, the only undesirable effects that were consistently considered to be related to NEUPOGEN administration were musculoskeletal pain, predominantly mild to moderate bone pain and myalgia. The incidence of these events was similar to that reported in cancer patients.

Splenic enlargement was reported to be related to NEUPOGEN therapy in < 3% of patients. In all cases this was mild or moderate on physical examination and the clinical course was benign; no patients had a diagnosis of hypersplenism and no patients underwent splenectomy. As splenic enlargement is a common finding in patients with HIV infection and is present to varying degrees in most patients with AIDS, the relationship to NEUPOGEN treatment is unclear.

Frequency	**Body System**	**Undesirable Effect**
Very Common (> 10%)	Musculoskeletal	Musculoskeletal Pain
Common (1 – 10%)	Haematological	Spleen Disorder

4.9 Overdose

The effects of NEUPOGEN overdosage have not been established. Discontinuation of NEUPOGEN 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: Cytokines, ATC Code: L03AA02

Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. NEUPOGEN containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within twenty-four hours, with minor increases in monocytes. In some severe chronic neutropenia patients filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose-dependent at recommended doses. Neutrophils produced 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.

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

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

Recipients of allogeneic peripheral blood progenitor cells mobilised with NEUPOGEN experienced significantly more rapid haematological recovery, leading to a significant decrease in time to unsupported platelet recovery when compared with allogeneic bone marrow transplantation.

Use of filgrastim for the mobilisation of peripheral blood progenitor cells in normal donors prior to allogeneic peripheral blood progenitor cell transplantation

In normal donors, a 10 μg/kg/day dose administered subcutaneously for 4 to 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 severe chronic neutropenia (severe congenital, cyclic, and idiopathic neutropenia) induces a sustained increase in absolute neutrophil counts in peripheral blood and a reduction of infection and related events.

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

As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells.

5.2 Pharmacokinetic properties

Clearance of filgrastim has been shown to follow first-order pharmacokinetics after both subcutaneous and intravenous 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 NEUPOGEN 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. 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 to 16 hours. The volume of distribution in blood is approximately 150 ml/kg.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Acetate

Sorbitol

Polysorbate 80

Water for Injections

Sodium acetate is formed by titrating glacial acetic acid with sodium hydroxide

6.2 Incompatibilities

NEUPOGEN should not be diluted with saline solutions.

Diluted filgrastim may be adsorbed to glass and plastic materials.

This medicinal product must not be mixed with other products except those mentioned in section 6.6 (Instructions for use and handling, and disposal).

6.3 Shelf life

30 months

Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2 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 to 8°C, unless dilution has taken place in controlled and validated aseptic

conditions.

6.4 Special precautions for storage

Store at 2°C to 8°C.

Diluted NEUPOGEN solution should be stored at 2 to 8°C

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

6.5 Nature and contents of container

Package containing one or five pre-filled syringe(s) of 0.5 ml NEUPOGEN solution for injection.

The pre-filled syringes are made from type I glass and have a permanently attached stainless steel needle in the tip. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See Section 4.4.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If required, NEUPOGEN 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 solution Ph. Eur. added.

NEUPOGEN contains no preservative. In view of the possible risk of microbial contamination, NEUPOGEN syringes are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

When diluted in 5% glucose solution, NEUPOGEN is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.

Minervum 7061

4817 ZK Breda

The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

PL 16216/0043

PL 16216/0044

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2003

10. DATE OF REVISION OF THE TEXT

12 January 2007

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