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Date: 21st August 2013

**Direct Health Care Professional communication**

**Filgrastim (Neupogen®) is associated with a risk of capillary leak syndrome in patients with cancer and in healthy donors**

**Pegfilgrastim (Neulasta®) is associated with a risk of capillary leak syndrome in patients with cancer**

**Dear Healthcare Professional,**

Amgen Inc., in agreement with the European Medicines Agency and the Irish Medicines Board, would like to inform you about an adverse effect of capillary leak syndrome (CLS) associated with filgrastim and pegfilgrastim.

**Summary**

- **CLS has been reported in recipients of filgrastim including patients undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor cell mobilisation.**
- **CLS has been reported in recipients of pegfilgrastim undergoing chemotherapy.**
- **Episodes vary in severity and frequency and may be fatal. CLS is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration.**
- **Healthcare professionals should closely monitor for CLS symptoms in patients and healthy donors receiving filgrastim or pegfilgrastim. Standard symptomatic treatment should be given immediately if symptoms occur (this may include intensive care).**
- **Patients and healthy donors should be advised to contact their doctor immediately if they develop symptoms (often with rapid onset) such as generalised body swelling, puffiness (which may be associated with passing water less frequently), difficulty breathing, abdominal swelling and tiredness.**
- **The benefits of filgrastim and pegfilgrastim continue to outweigh any risks in the approved indications.**

## Further information on the safety concern

CLS has been reported in patients with cancer undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor cell mobilisation who were receiving the granulocyte colony-stimulating factor (G-CSF) products filgrastim or pegfilgrastim. Reports have generally involved people with advanced malignant diseases, sepsis, those taking multiple chemotherapy medications or those undergoing aphaeresis. The mechanism of CLS remains unclear.

For filgrastim, 34 post-marketing reports of CLS were received world-wide between April 1991 and August 2012. Of these, one case concerned a healthy donor undergoing stem cell mobilisation and apheresis. In 12 cases, there was a positive de-challenge with supportive treatment or corticosteroids. In the majority of cases, the CLS symptoms occurred after the first dose of filgrastim treatment. In 2 cases the symptoms occurred after the first dose with a positive re-challenge during the second dose. Six cases had a fatal outcome from CLS.

For pegfilgrastim, 4 post-marketing reports of CLS were received world-wide between August 2002 and August 2012. CLS symptoms appeared after the second dose of pegfilgrastim in 2 cases. In 1 of these cases CLS occurred one day after pegfilgrastim, suggesting a temporal association. In another case, the patient had a fatal outcome from CLS.

The total number of CLS reports expressed above have been seen in over 8.5 million patients exposed to filgrastim and over 4 million patients exposed to pegfilrastim in the post-marketing setting.

The Summaries of Product Characteristics and Patient Information Leaflets for filgrastim and pegfilgrastim have been updated to reflect the new safety information [see Annexe].

## Call for reporting

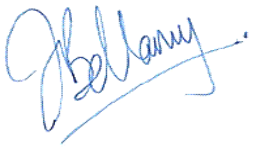
Healthcare professionals should report any adverse reactions suspected to be associated with the use of filgrastim or pegfilgrastim products to the Irish Medicines Board using a Yellow Card obtained from the Irish Medicines Board or electronically via the online reporting system at *www.imb.ie*. Adverse reactions can also be reported to the Irish Medicines Board by calling on (01) 676 4971.

Additionally, any such information may be reported to Amgen Europe B.V. by contacting Amgen UK/Ireland Drug Safety Department directly on 0044 1223 436712.

## Company contact point

Should you have any questions or require additional information regarding the use of Neupogen® and/or Neulasta®, please contact Amgen UK/Ireland Medical Information on 0044 1223 436441 or by email to gbinfoline@amgen.com.

Sincerely,



Dr Steven Bellamy MBChB, Medical Director UK & Ireland

Annexe: Updated Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs). Note on Neupogen®: Only the updated Neupogen® Singleject 30 MU solution for injection pre-filled syringe SmPC and Neupogen® Singleject 30 MU and 48 MU solution for injection pre-filled syringe PIL are appended to this communication. The information in this communication is applicable to all Neupogen® strengths and presentations.

**NEUPOGEN® (filgrastim)** Brief Prescribing Information

Please refer to the Summary of Product Characteristics before prescribing Neupogen. **Pharmaceutical Form:** Neupogen is a sterile, clear, colourless solution for subcutaneous (SC) or intravenous (IV) use presented in vials (containing 300 micrograms (mcg) of filgrastim) and pre-filled syringes (containing 300 or 480 mcg of filgrastim) for single dose use only. **Indications:** Reduction in duration of neutropenia and incidence of febrile neutropenia after established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes); reduction in duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. Mobilisation of peripheral blood progenitor cells (PBPCs). Long-term treatment to increase neutrophil counts and reduce incidence and duration of infection-related events in patients (children or adults) with severe congenital neutropenia (SCN), cyclic, or idiopathic neutropenia with absolute neutrophil count (ANC) $\leq 0.5 \times 10^9$/L, and history of severe or recurrent infections. Treatment of persistent neutropenia (ANC $\leq 1.0 \times 10^9$/L) in patients with advanced HIV infection, when other options to manage neutropenia are inappropriate. **Dosage and Administration:** The first dose of Neupogen should not be administered less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow infusion. Established cytotoxic chemotherapy: 5 mcg/kg/day by sc injection, or by iv infusion over 30 minutes. Daily dosing should continue until the expected nadir has passed and the neutrophil count has recovered to the normal range. Myeloablative therapy followed by bone marrow transplantation: starting dose 10 mcg/kg/day given as a 30 minute or 24 hour iv infusion, or as a 24 hour continuous sc infusion. Once the neutrophil nadir has passed, titrate daily dose against neutrophil response. If titration is required, see Summary of Product Characteristics. Mobilisation of PBPCs in patients: Alone: 10 mcg/kg/day sc either as a 24 hour infusion or as a single sc daily injection for 5 to 7 consecutive days. Following myelosuppressive chemotherapy: 5 mcg/kg/day sc injection given daily from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Normal Donors: 10 mcg/kg/day sc for 4 to 5 consecutive days. Severe Chronic Neutropenias: Congenital: starting dose 12 mcg/kg/day sc as single or divided doses. Idiopathic or Cyclic: starting dose 5 mcg/kg/day sc as single or divided doses. Dosage adjustment: Continue treatment until neutrophil count can be maintained at $>1.5 \times 10^9$/L, then ascertain minimum effective dose required to maintain this level. After 1-2 weeks therapy, initial dose may be doubled or halved depending on response; dose may be individually adjusted every 1-2 weeks thereafter to maintain average neutrophil count between $1.5 \times 10^9$/L and $10 \times 10^9$/L. For severe infections a faster dose escalation may be considered but long-term safety of Neupogen administration above 24 mcg/kg/day in patients with SCN has not been established. Other particulars: Dose adjustment not required in patients with severe renal or hepatic impairment. Paediatric patients: 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. There were no differences in the safety profiles for paediatric patients in the SCN trial program. Patients with HIV infection: Reversal of neutropenia: starting dose 1 mcg/kg/day by sc injection with titration up to a maximum of 4 mcg/kg/day until a normal neutrophil count is reached and can be maintained (ANC $> 2.0 \times 10^9$/L). Maintaining normal neutrophil counts: minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 300 mcg/day by sc injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC (long-term administration may be required). **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients. **Special Warnings and Precautions:** Not for escalation of cytotoxic chemotherapy doses above established regimens. Neupogen should not be administered to patients with SCN who develop leukemia or have evidence of leukaemic evolution. Malignant cell growth: Safety and efficacy not established in patients with myelodysplastic syndrome or chronic myelogenous leukaemia. Neupogen is not indicated in these conditions. Administer Neupogen with caution in secondary AML. Safety and efficacy not established in *de novo* AML patients <55 years with good cytogenetics (t(8;21), t(15;17) and inv(16)). 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. The onset of pulmonary signs (cough, fever, dyspnoea) in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). Patients with a recent history of lung infiltrates or pneumonia may be at higher risk. Discontinue Neupogen and give appropriate treatment. Capillary leak syndrome (CLS) has been reported after granulocyte-colony stimulating factor (G-CSF) administration, and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of CLS should be closely monitored and receive standard symptomatic treatment. CLS can be life threatening if treatment is delayed. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex) which may cause allergic reactions. Cancer patients: White blood cell count should be performed at regular intervals during Neupogen therapy. If leukocyte counts exceed $50 \times 10^9$/l after the expected nadir, Neupogen should be discontinued immediately. Regular monitoring of platelet count and haematocrit is recommended. Neutrophil precursors may be reduced in patients who have received extensive prior chemotherapy or radiotherapy, therefore neutrophil response to Neupogen may be diminished. Vascular disorders, including veno-occlusive disease and fluid volume disturbances, 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-CSFs after allogeneic bone marrow transplantation. PBPC mobilisation: No direct clinical benefit to normal donors, therefore only consider procedure for allogeneic stem cell transplantation. Neupogen safety and efficacy not assessed in normal donors <16 years or >60 years. Transient thrombocytopenia (platelets <100 x $10^9$/L) following filgrastim administration and leukapheresis observed in 35% of subjects studied. Discontinue or reduce Neupogen dosage if leukocyte counts rise to >70 x $10^9$/L. Monitor donors until haematological indices return to normal. A risk of promotion of a malignant myeloid clone cannot be excluded. Uncommon cases of splenic rupture have been reported including fatal cases in healthy donors (and patients) following administration of G-CSFs. Monitor spleen size; consider diagnosis of splenic rupture in donors (and/or patients) reporting left upper abdominal pain or shoulder tip pain. In case of suspected or confirmed pulmonary adverse events, discontinuation of Neupogen should be considered. SCN patients: Monitor platelets closely especially in first few weeks of Neupogen therapy. Consider dose reduction or intermittent cessation of Neupogen treatment if platelet count is consistently <100,000 /$mm^3$. Blood cell counts should be monitored closely. Evaluation of bone morphology and karyoptype should be performed prior to treatment and following treatment at regular intervals (approximately every 12 months). Exclude viral infections as cause of transient neutropenia. Spleen size should be evaluated regularly. Regular urinalysis advised to monitor for haematuria and proteinuria. Patients with HIV infection: Monitor ANC closely; daily for first 2-3 days, then at least twice a week for first two weeks, then once a week or once every other week during maintenance therapy. Patients may be at higher risk of developing thrombocytopenia and anaemia. Regular monitoring of blood counts is recommended. Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In these patients, consider appropriate treatment of the underlying condition, in addition to Neupogen treatment for neutropenia. Sickle Cell Disease: Exercise caution when administering Neupogen to patients with Sickle Cell Disease as Sickle cells crises, in some cases fatal have been reported. Evaluation of the potential risks and benefits should be performed. All patients: Neupogen contains sorbitol (50mg/mL). Patients with rare hereditary problems of fructose intolerance should not take this medicine. Neupogen contains less than 1 mmol (23 mg) sodium per 0.6 mg/ml, i.e. essentially sodium free. In order to improve the traceability of G-CSFs, the trade name of the administered product should be clearly recorded in the patient file. **Interactions:** Not recommended in the period 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. Lithium likely to potentiate effect of Neupogen. **Pregnancy:** The safety of Neupogen has not been established in pregnant women. Evaluation of the potential risks to the foetus and expected therapeutic benefit should be performed. Not recommended in nursing women. **Adverse effects:** Clinical trials and/or post-marketing: Hypersensitivity-type reactions including anaphylaxis, rash, urticaria, angioedema, dyspnoea and hypotension have been reported. Neupogen should be permanently discontinued in patients who experience a serious allergic reaction. 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 ARDS, which may be fatal. Uncommon cases of splenic rupture have been reported. Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥ 1/1000 to < 1/100) in cancer patients undergoing chemotherapy and healthy donors undergoing PBPC mobilisation following administration of G-CSFs. Cancer patients: very common (≥ 1/10) and common (≥ 1/100 to < 1/10) adverse reactions include blood uric acid increased, blood lactate dehydrogenase increased, anorexia (decreased appetite), headache, hypotension, pharyngolaryngeal pain (oropharyngeal pain), cough, dyspnoea, haemoptysis, diarrhoea, vomiting, constipation, nausea, gamma-glutamyl transferase increased, blood alkaline phosphatase increased, rash, alopecia, musculoskeletal pain (includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal chest pain, neck pain), dysuria, asthenia, fatigue, mucosal inflammation, chest pain. There have been reports of GvHD and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation. In the post-marketing setting there have been reports of cutaneous vasculitis, Sweet's Syndrome (acute febrile dermatosis), and isolated cases of sickle cell crises have been reported in patients with sickle cell disease. The frequency of these adverse reactions is estimated as uncommon from clinical trial data. Pseudogout has been reported, the frequency is estimated as uncommon from clinical trial data. PBPC mobilisation in normal donors: very common (≥ 1/10) and common (≥ 1/100 to < 1/10) adverse reactions include thrombocytopenia, leukocytosis, blood lactate dehydrogenase increased, blood alkaline phosphatase increased, headache, dyspnoea, musculoskeletal pain (includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal chest pain, neck pain). Common but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture have been reported. Pulmonary adverse events (haemoptysis, pulmonary haemorrhage, lung infiltration, dyspnoea and hypoxia) have been reported. Exacerbation of arthritic symptoms has been observed uncommonly. SCN patients: very common (≥ 1/10) and common (≥ 1/100 to < 1/10) adverse reactions include splenomegaly (may be progressive in a minority of cases), anaemia, thrombocytopenia, hyperuricaemia, blood glucose decreased, blood lactate dehydrogenase increased, headache, epistaxis, diarrhoea, blood alkaline phosphatase increased, hepatomegaly, rash, cutaneous vasculitis, alopecia, musculoskeletal pain (includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal chest pain, neck pain), arthralgia, osteoporosis, haematuria, injection site reaction. During long term use cutaneous vasculitis has been reported in 2% of SCN patients. Cases of decreased bone density and osteoporosis have been reported in

paediatric patients with SCN receiving chronic treatment with Neupogen. The frequency is estimated as common from clinical trial data. Patients with HIV infection: very common (≥ 1/10) and common (≥ 1/100 to < 1/10) adverse reactions include musculoskeletal pain (includes bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal chest pain, neck pain) and splenomegaly. Please consult the Summary of Product Characteristics for a full description of adverse reactions. **Legal Category:** POM. **Presentation and Basic Cost:** 0.5 ml pre-filled syringe containing 30 MU (300 mcg) filgrastim. 0.5 ml pre-filled syringe containing 48 MU (480 mcg) of filgrastim. 1 ml vial containing 30 MU (300 mcg) filgrastim. Prices in the Republic of Ireland are available on request **Product Licence Numbers:** Syringes 30 MU PA 1026/1/7, Syringes 48 MU PA 1026/1/8, Vials 30 MU PA 1026/1/1. **Product Licence Holder:** Amgen Europe B.V., Minervum 7061, 4817 ZK Breda, The Netherlands. NEUPOGEN is a registered trademark of Amgen Inc. Full prescribing information is available on request. Date of preparation August 2013 Ref: NGO-IRL-AMG-226-2013-P.

Adverse events should be reported to Amgen Limited on +44 (0) 1223 436712

# NEULASTA® (pegfilgrastim)

**Brief Prescribing Information**

Please refer to the Summary of Product Characteristics before prescribing Neulasta. **Pharmaceutical Form:** Pre-filled syringe containing 6 mg of pegfilgrastim in 0.6 ml solution for injection, for single dose use only. **Indication:** Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). **Dosage and Administration:** 6 mg Neulasta for each chemotherapy cycle administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy. Experience in children is limited. Therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. **Contra-indications:** Hypersensitivity to the active substance or to any excipients. **Special Warnings and Precautions:** Limited data suggest a similar effect on time to recovery of severe neutropenia for Neulasta to filgrastim in patients with *de novo* acute myeloid leukaemia (AML). Long term effects have not been established, and Neulasta should be used with caution in the AML patient population. Neulasta should not be used in patients with myelodysplastic syndrome, chronic myelogenous leukaemia or secondary AML. Safety and efficacy not evaluated in *de novo* AML patients aged <55 years with cytogenetics t(15;17). Patients with a recent history of pulmonary infiltrates may be at higher risk of pulmonary adverse events such as interstitial pneumonia. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS). In such circumstances, Neulasta should be discontinued at the discretion of the physician and the appropriate treatment given. Capillary leak syndrome (CLS) has been reported after granulocyte-colony stimulating factor (G-CSF) administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of CLS should be closely monitored and receive standard symptomatic treatment. CLS can be life-threatening if treatment is delayed. Cases of splenic rupture have been reported including fatal cases following administration of Neulasta. Monitor spleen size; consider diagnosis of splenic rupture in patients reporting left upper abdominal pain or shoulder tip pain. Treatment with Neulasta alone does not preclude thrombocytopenia and anaemia. Regular monitoring of platelet count and haematocrit is recommended. Neulasta should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens. Exercise caution when administering Neulasta in patients with sickle cell disease, and appropriate monitoring, due to the possible association of Neulasta with splenic enlargement and vaso-occlusive crisis. White blood cell (WBC) counts of 100 x $10^9$/l or greater have been observed in less than 1% of patients receiving Neulasta, but no directly attributable adverse events have been reported. A WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x $10^9$/l after the expected nadir, Neulasta should be discontinued immediately. If a serious allergic reaction occurs, appropriate therapy should be administered. Neulasta should be permanently discontinued in patients who experience a serious allergic reaction. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex) which may cause allergic reactions. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Neulasta contains less than 1 mmol (23 mg) sodium per 0.6 mg/ml, i.e. essentially sodium free. **Interactions:** In animal models, concomitant administration of Neulasta and 5-Fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression. Lithium could potentiate the effect of Neulasta. **Pregnancy and lactation:** No adequate experience in human pregnancy and lactation. Neulasta should not be used during pregnancy unless clearly necessary. Do not administer to women who are breast-feeding. **Undesirable Effects:** Hypersensitivity-type reactions, including skin rash, urticaria, angioedema, dyspnoea, erythaema, flushing, and hypotension have been reported. Serious allergic reactions, including anaphylaxis can occur in patients receiving Neulasta. Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported rarely in cancer patients undergoing chemotherapy following administration of G-CSFs. Splenomegaly generally asymptomatic and cases of splenic rupture including some fatal cases have been reported. Spleen size should be closely monitored (clinical examination, ultrasound). Pulmonary adverse effects including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Uncommonly, cases have resulted in respiratory failure or Adult Respiratory Distress Syndrome, which may be fatal. Isolated cases of sickle cell crises have been reported in patients with sickle cell disease. Very common (≥ 1/10) adverse reactions were mild to moderate bone pain and musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, neck pain), nausea and headache. Common adverse reactions (≥ 1/100 to < 1/10) include thrombocytopenia and injection site reactions. Uncommon adverse reactions (≥ 1/1000 to < 1/100) include Sweet's syndrome, cutaneous vasculitis, cases of leukocytosis (White Blood Count > 100 x $10^9$/l), elevations in uric acid, elevations in lactate dehydrogenase and alkaline phosphatase, transient elevations in liver function tests for alanine aminotransferase or aspartate aminotransferase. Please consult the Summary of Product Characteristics for a full description of adverse reactions. **Pharmaceutical Precautions:** Neulasta is incompatible with sodium chloride solutions. Store at 2°C to 8°C (in a refrigerator). Neulasta may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Neulasta left at room temperature for more than 72 hours should be discarded. Do not freeze. Accidental exposure to freezing temperatures for a single period of less than 24 hours does not adversely affect the stability of Neulasta. Keep container in outer carton to protect from light. **Legal Category:** POM. **Presentation, Basic Costs and Marketing Authorisation Number:** Neulasta 6 mg: Blistered syringe with needleguard; EU/1/02/227/004. Prices in the Republic of Ireland are available on

request. **Marketing Authorisation Holder:** Amgen Europe B.V., Minervum 7061, 4817 ZK Breda, The Netherlands. Further information is available from Amgen Limited, 240 Cambridge Science Park, Milton Road, Cambridge, CB4 0WD, UK. **Date of PI preparation:** August 2013 (NO-IRL-AMG-225-2013-P).

**Adverse events should be reported to Amgen Limited on +44 (0) 1223 436712**