ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neupopeg 6 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 6 mg of pegfilgrastim* in 0.6 ml solution for injection.
The concentration is 10 mg/ml based on protein only**.

*Produced in *Escherichia coli* cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG).
** The concentration is 20 mg/ml if the PEG moiety is included

The potency of this product should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1.

Excipients:

Excipients known to have a recognised action: sorbitol E420, sodium acetate (see section 4.4).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

4.2 Posology and method of administration

Neupopeg therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.

One 6 mg dose (a single pre-filled syringe) of Neupopeg is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy.

Neupopeg is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy.

Renal impairment: no dose change is recommended in patients with renal impairment, including those with end stage renal disease.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Limited clinical data suggest a comparable effect on time to recovery of severe neutropenia for pegfilgrastim to filgrastim in patients with *de novo* acute myeloid leukaemia (see section 5.1). However, the long-term effects of Neupopeg have not been established in acute myeloid leukaemia; therefore, it should be used with caution in this patient population.

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 Neupopeg have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary Acute Myeloid Leukaemia (AML); therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

The safety and efficacy of Neupopeg administration in *de novo* AML patients aged < 55 years with cytogenetics t(15;17) have not been established.

The safety and efficacy of Neupopeg have not been investigated in patients receiving high dose chemotherapy.

Rare (≥ 1/10,000 to < 1/1,000) 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 along with increased neutrophil count may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS). In such circumstances Neupopeg should be discontinued at the discretion of the physician and the appropriate treatment given.

Common (≥ 1/100 to < 1/10) but generally asymptomatic cases of splenomegaly and very rare (< 1/10,000) cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Treatment with Neupopeg alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and haematocrit is recommended.

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

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Therefore, physicians should exercise caution when administering Neupopeg in patients with sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of Neupopeg with splenic enlargement and vaso-occlusive crisis.

White blood cell counts of 100 x 10^9/l or greater have been observed in less than 1% of patients receiving Neupopeg. No adverse events directly attributable to this degree of leukocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of Neupopeg.

The safety and efficacy of Neupopeg for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.

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

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.

Neupopeg contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine**.**

Neupopeg contains less than 1 mmol (23 mg) sodium per 6 mg dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Neupopeg should be administered approximately 24 hours after administration of cytotoxic chemotherapy. In clinical studies, Neupopeg has been safely administered 14 days before chemotherapy. Concomitant use of Neupopeg with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of Neupopeg and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

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

The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

The safety and efficacy of Neupopeg have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression e.g., nitrosoureas.

Specific interaction or metabolism studies have not been performed, however, clinical studies have not indicated an interaction of Neupopeg with any other medicinal products.

4.6 Pregnancy and lactation

There are no adequate data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Neupopeg should not be used during pregnancy unless clearly necessary.

There is no clinical experience with breast-feeding women, therefore Neupopeg should not be administered to women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In randomised clinical studies in patients with malignancy receiving Neupopeg after cytotoxic chemotherapy, most adverse events were caused by the underlying malignancy or cytotoxic chemotherapy.

The most frequently reported and very common study-drug related undesirable effect was bone pain Bone pain was generally of mild-to-moderate severity, transient and could be controlled in most patients with standard analgesics.

Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea, hypotension, injection site reactions, erythaema and flushing, occurring on initial or subsequent treatment have been reported with Neupopeg. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Pegfilgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, were common (≥ 1/100 to < 1/10); reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were very common (≥ 1/10) in patients receiving Neupopeg following cytotoxic chemotherapy. Nausea was observed in healthy volunteers and patients receiving chemotherapy.

Common (≥ 1/100 to <1/10) but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see section 4.4). Other commonly reported undesirable effects include pain, injection site pain; chest pain (non-cardiac); headache; arthralgia; myalgia; back, limb, musculo-skeletal and neck pain.

Rare (≥ 1/10,000 to < 1/1,000) pulmonary adverse effects including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Some of the reported cases have resulted in respiratory failure or Adult Respiratory Distress Syndrome (ARDS), which may be fatal (see section 4.4)

Rare (≥ 1/10,000 to < 1/1,000) cases of thrombocytopenia and leukocytosis have been reported.

Rare (≥ 1/10,000 to < 1/1,000) cases of Sweet's syndrome have been reported, although in some cases underlying haematological malignancies may play a role.

Very rare (< 1/10,000) events of cutaneous vasculitis have been reported in patients treated with Neupopeg. The mechanism of vasculitis in patients receiving Neupopeg is unknown.

Very rare (< 1/10,000) elevations in liver function tests (LFTs) for ALT (alanine aminotransferase) or AST (aspartate aminotransferase), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.

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

4.9 Overdose

There is no experience with overdose of Neupopeg in humans.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytokines, ATC Code: L03AA13

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes

and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

In two randomised, double-blind, pivotal studies in patients with high risk stage II-IV breast cancer undergoing myelosuppressive chemotherapy consisting of doxorubicin and docetaxel, use of pegfilgrastim, as a single once per cycle dose, reduced the duration of neutropenia and the incidence of febrile neutropenia similarly to that observed with daily administrations of filgrastim (a median of 11 daily administrations). In the absence of growth factor support, this regimen has been reported to result in a mean duration of grade 4 neutropenia of 5 to7 days, and a 30-40% incidence of febrile neutropenia. In one study (n=157), which used a 6mg fixed dose of pegfilgrastim the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.8 days compared with 1.6 days in the filgrastim group (difference 0.23 days, 95% CI -0.15, 0.63). Over the entire study, the rate of febrile neutropenia was 13% of pegfilgrastim-treated patients compared with 20% of filgrastim-treated patients (difference 7%, 95% CI of -19%, 5%). In a second study (n=310), which used a weight-adjusted dose (100 micrograms/kg), the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.7 days, compared with 1.8 days in the filgrastim group (difference 0.03 days, 95% CI -0.36, 0.30). The overall rate of febrile neutropenia was 9% of patients treated with pegfilgrastim and 18% of patients treated with filgrastim (difference 9%, 95% CI of -16.8%,-1.1%).

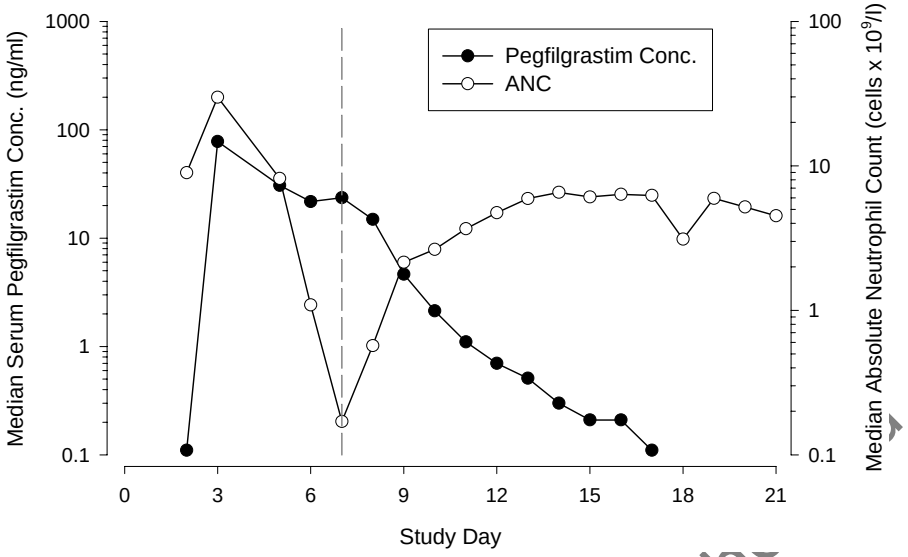
In a placebo-controlled, double blind study in patients with breast cancer the effect of pegfilgrastim on the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen associated with a febrile neutropenia rate of 10-20% (docetaxel 100 mg/m^2 every 3 weeks for 4 cycles). Nine hundred and twenty eight patients were randomised to receive either a single dose of pegfilgrastim or placebo approximately 24 hours (Day 2) after chemotherapy in each cycle. The incidence of febrile neutropenia was lower for patients randomised to receive pegfilgrastim compared with placebo (1% versus 17%, $p<0.001$). The incidence of hospitalisations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was lower in the pegfilgrastim group compared with placebo (1% versus 14%, $p<0.001$; and 2% versus 10%, $p<0.001$)

A small (n=83), Phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 22 days in both treatment groups. Long term outcome was not studied (see section 4.4).

5.2 Pharmacokinetic properties

After a single subcutaneous dose of pegfilgrastim, the peak serum concentration of pegfilgrastim occurs at 16 to 120 hours after dosing and serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy. The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery (see Figure 1).

Figure 1. Profile of Median Pegfilgrastim Serum Concentration and Absolute Neutrophil Count (ANC) in Chemotherapy Treated Patients after a Single 6 mg Injection



Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. In a open label, single dose study (n=31) various stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim.

Limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (> 65 years) is similar to that in adults.

5.3 Preclinical safety data

Preclinical data from conventional studies of repeated dose toxicity revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

There were no adverse effects observed in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal toxicity (embryo loss) at low subcutaneous doses. In rat studies, it was shown that pegfilgrastim may cross the placenta. The relevance of these findings for humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate*
Sorbitol (E420)
Polysorbate 20
Water for injections

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, particularly with sodium chloride solutions.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Neupopeg may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Neupopeg 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 Neupopeg.

Keep the container in the outer carton, in order to protect from light.

6.5 Nature and contents of container

0.6 ml of solution for injection in a pre-filled syringe (Type I glass), with a rubber stopper, and with a stainless steel needle. Pack size of one, in either blistered or non-blistered packaging. Single use only.

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

Before administration, Neupopeg solution should be inspected visually for particulate matter. Only a solution that is clear and colourless should be injected.

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive.

Allow the pre-filled syringe to reach room temperature before injecting.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/228/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2002
Date of last renewal: 16 July 2007

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Neupopeg 6 mg solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 6 mg of pegfilgrastim* in 0.6 ml solution for injection. The concentration is 10 mg/ml based on protein only**.

*Produced in *Escherichia coli* cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG).
** The concentration is 20 mg/ml if the PEG moiety is included

The potency of this product should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section 5.1

Excipients:

Excipients known to have a recognised action: sorbitol E420, sodium acetate (see section 4.4).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen (SureClick).

Clear, colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

4.2 Posology and method of administration

Neupopeg therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.

One 6 mg dose (a single pre-filled pen) of Neupopeg (SureClick) is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy.

Neupopeg is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy.

Renal impairment: no dose change is recommended in patients with renal impairment, including those with end stage renal disease.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Limited clinical data suggest a similar effect on time to recovery of severe neutropenia for pegfilgrastim to filgrastim in patients with *de novo* acute myeloid leukaemia (see section 5.1). However, the long-term effects of Neupopeg have not been established in acute myeloid leukaemia; therefore, it should be used with caution in this patient population.

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 Neupopeg have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary Acute Myeloid Leukaemia (AML); therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

The safety and efficacy of Neupopeg administration in *de novo* AML patients aged < 55 years with cytogenetics t(15;17) have not been established.

The safety and efficacy of Neupopeg have not been investigated in patients receiving high dose chemotherapy.

Rare (≥ 1/10,000 to < 1/1,000) 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 along with increased neutrophil count may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS). In such circumstances Neupopeg should be discontinued at the discretion of the physician and the appropriate treatment given.

Common (≥ 1/100 to < 1/10) but generally asymptomatic cases of splenomegaly and very rare (< 1/10,000) cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Treatment with Neupopeg alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and haematocrit is recommended.

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

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Therefore, physicians should exercise caution when administering Neupopeg in patients with sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of Neupopeg with splenic enlargement and vaso-occlusive crisis.

White blood cell counts of 100 x 10^9/l or greater have been observed in less than 1% of patients receiving Neupopeg. No adverse events directly attributable to this degree of leukocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of Neupopeg.

The safety and efficacy of Neupopeg for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.

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

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.

Neupopeg contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine**.**

Neupopeg contains less than 1 mmol (23 mg) sodium per 6 mg dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Neupopeg should be administered approximately 24 hours after administration of cytotoxic chemotherapy. In clinical studies, Neupopeg has been safely administered 14 days before chemotherapy. Concomitant use of Neupopeg with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of Neupopeg and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

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

The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

The safety and efficacy of Neupopeg have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression e.g., nitrosoureas.

Specific interaction or metabolism studies have not been performed, however, clinical studies have not indicated an interaction of Neupopeg with any other medicinal products.

4.6 Pregnancy and lactation

There are no adequate data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Neupopeg should not be used during pregnancy unless clearly necessary.

There is no clinical experience with breast-feeding women, therefore Neupopeg should not be administered to women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In randomised clinical studies in patients with malignancy receiving Neupopeg after cytotoxic chemotherapy, most adverse events were caused by the underlying malignancy or cytotoxic chemotherapy.

The most frequently reported and very common study-drug related undesirable effect was bone pain Bone pain was generally of mild-to-moderate severity, transient and could be controlled in most patients with standard analgesics.

Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea, hypotension, injection site reactions, erythaema and flushing, occurring on initial or subsequent treatment have been reported with Neupopeg. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Pegfilgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, were common (≥ 1/100 to < 1/10); reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were very common (≥ 1/10) in patients receiving Neupopeg following cytotoxic chemotherapy. Nausea was observed in healthy volunteers and patients receiving chemotherapy.

Common (≥ 1/100 to <1/10) but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see section 4.4). Other commonly reported undesirable effects include pain, injection site pain; chest pain (non-cardiac); headache; arthralgia; myalgia; back, limb, musculo-skeletal and neck pain.

Rare (≥ 1/10,000 to < 1/1,000) pulmonary adverse effects including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Some of the reported cases have resulted in respiratory failure or Adult Respiratory Distress Syndrome (ARDS), which may be fatal (see section 4.4)

Rare (≥ 1/10,000 to < 1/1,000) cases of thrombocytopenia and leukocytosis have been reported.

Rare (≥ 1/10,000 to < 1/1,000) cases of Sweet's syndrome have been reported, although in some cases underlying haematological malignancies may play a role.

Very rare (< 1/10,000) events of cutaneous vasculitis have been reported in patients treated with Neupopeg. The mechanism of vasculitis in patients receiving Neupopeg is unknown.

Very rare (< 1/10,000) elevations in liver function tests (LFTs) for ALT (alanine aminotransferase) or AST (aspartate aminotransferase), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.

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

4.9 Overdose

There is no experience with overdose of Neupopeg in humans.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytokines, ATC Code: L03AA13

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes

and/or lymphocytes. Similarly to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

In two randomised, double-blind, pivotal studies in patients with high risk stage II-IV breast cancer undergoing myelosuppressive chemotherapy consisting of doxorubicin and docetaxel, use of pegfilgrastim, as a single once per cycle dose, reduced the duration of neutropenia and the incidence of febrile neutropenia similarly to that observed with daily administrations of filgrastim (a median of 11 daily administrations). In the absence of growth factor support, this regimen has been reported to result in a mean duration of grade 4 neutropenia of 5 to7 days, and a 30-40% incidence of febrile neutropenia. In one study (n=157), which used a 6mg fixed dose of pegfilgrastim the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.8 days compared with 1.6 days in the filgrastim group (difference 0.23 days, 95% CI -0.15, 0.63). Over the entire study, the rate of febrile neutropenia was 13% of pegfilgrastim-treated patients compared with 20% of filgrastim-treated patients (difference 7%, 95% CI of -19%, 5%). In a second study (n=310), which used a weight-adjusted dose (100 microgramsg/kg), the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.7 days, compared with 1.8 days in the filgrastim group (difference 0.03 days, 95% CI -0.36, 0.30). The overall rate of febrile neutropenia was 9% of patients treated with pegfilgrastim and 18% of patients treated with filgrastim (difference 9%, 95% CI of -16.8%,-1.1%).

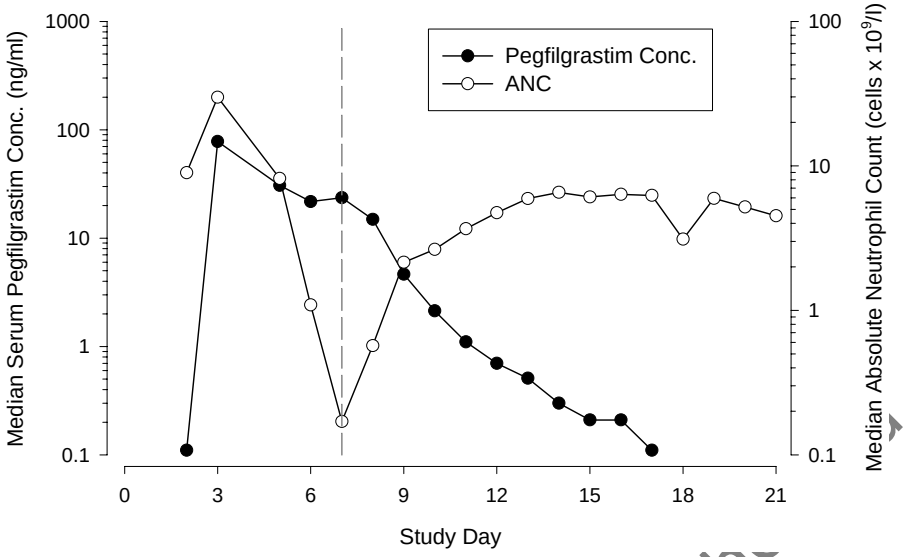
In a placebo-controlled, double blind study in patients with breast cancer the effect of pegfilgrastim on the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen associated with a febrile neutropenia rate of 10-20% (docetaxel 100 mg/m^2 every 3 weeks for 4 cycles). Nine hundred and twenty eight patients were randomised to receive either a single dose of pegfilgrastim or placebo approximately 24 hours (Day 2) after chemotherapy in each cycle. The incidence of febrile neutropenia was lower for patients randomised to receive pegfilgrastim compared with placebo (1% versus 17%, $p<0.001$). The incidence of hospitalisations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was lower in the pegfilgrastim group compared with placebo (1% versus 14%, $p<0.001$; and 2% versus 10%, $p<0.001$)

A small (n=83), Phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 22 days in both treatment groups. Long term outcome was not studied (see section 4.4).

5.2 Pharmacokinetic properties

After a single subcutaneous dose of pegfilgrastim, the peak serum concentration of pegfilgrastim occurs at 16 to 120 hours after dosing and serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy. The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery (see Figure 1).

Figure 1. Profile of Median Pegfilgrastim Serum Concentration and Absolute Neutrophil Count (ANC) in Chemotherapy Treated Patients after a Single 6 mg Injection



Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. In a open label, single dose study (n=31) various stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim.

Limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (> 65 years) is similar to that in adults.

5.3 Preclinical safety data

Preclinical data from conventional studies of repeated dose toxicity revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

There were no adverse effects observed in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal toxicity (embryo loss) at low subcutaneous doses. In rat studies, it was shown that pegfilgrastim may cross the placenta. The relevance of these findings for humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate*
Sorbitol (E420)
Polysorbate 20
Water for injections

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, particularly with sodium chloride solutions.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Neupopeg may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Neupopeg 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 Neupopeg.

Keep the container in the outer carton, in order to protect from light.

6.5 Nature and contents of container

The syringe inside the pen is made from Type I glass with a rubber stopper, and with a stainless steel needle; it contains 0.6 ml of solution for injection. Pack size of one, for single use only.

The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

6.6 Special precautions for disposal and other handling

The carton contains a package leaflet with the full instructions for use and handling.

Before administration, Neupopeg solution should be inspected visually for particulate matter. Only a solution that is clear and colourless should be injected. Each pen may only be used once.

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive.

Allow the pre-filled pen to reach room temperature before injecting.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/228/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2002
Date of last renewal: 16 July 2007

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Amgen Inc.
One Amgen Center Drive
Thousand Oaks
CA 91320
USA

Amgen Manufacturing Limited
P.O Box 4060
Road 31 km. 24.6
Juncos
Puerto Rico 00777-4060
USA

Name and address of the manufacturer responsible for batch release

Amgen Europe BV
Minervum 7061
NL-4817 ZK Breda
The Netherlands

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Neupopeg 6 mg solution for injection
Pegfilgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 6 mg of pegfilgrastim in 0.6 ml (10 mg/ml) solution for injection.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate, sorbitol (E420), polysorbate 20, water for injections.

Excipients known to have a recognised action: sorbitol (E420), sodium acetate.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a single use pre-filled syringe (0.6 ml). Pack size of one.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid vigorous shaking.

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the container in the outer carton, in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/228/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupopeg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK WITH SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Neupopeg 6 mg injection
Pegfilgrastim

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED SYRINGE LABEL

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

Neupopeg 6 mg
Pegfilgrastim
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

UNBLISTERED SYRINGE OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Neupopeg 6 mg solution for injection
Pegfilgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 6 mg of pegfilgrastim in 0.6 ml (10 mg/ml) solution for injection.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate, sorbitol (E420), polysorbate 20, water for injections.

Excipients known to have a recognised action: sorbitol (E420), sodium acetate.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a single use pre-filled syringe (0.6 ml). Pack size of one.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the container in the outer carton, in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/228/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupopeg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

UNBLISTERED SYRINGE LABEL

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

Neupopeg 6 mg injection
Pegfilgrastim
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Neupopeg 6 mg solution for injection in a pre-filled pen
Pegfilgrastim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 6 mg of pegfilgrastim in 0.6 ml (10 mg/ml) solution for injection.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate, sorbitol (E420), polysorbate 20, water for injections.

Excipients known to have a recognised action: sorbitol (E420), sodium acetate.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a single use pre-filled pen (0.6 ml). Pack size of one.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid vigorous shaking.

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the container in the outer carton, in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/228/003

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Neupopeg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

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

Neupopeg 6 mg injection
Pegfilgrastim
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

Dompé Biotec S.p.A.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupopeg 6 mg solution for injection in a pre-filled syringe
pegfilgrastim

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. WHAT NEUPOPEG IS AND WHAT IT IS USED FOR

Neupopeg is used to reduce the duration of neutropenia (low white blood cell count) and the occurrence of febrile neutropenia (low white blood cell count with a fever) which can be caused by the use of cytotoxic chemotherapy (medicines that destroy rapidly growing cells). White blood cells are important as they help your body fight infection. These cells are very sensitive to the effects of chemotherapy which can cause the number of these cells in your body to decrease. If white blood cells fall to a low level there may not be enough left in the body to fight bacteria and you may have an increased risk of infection.

Your doctor has given you Neupopeg to encourage your bone marrow (part of the bone which makes blood cells) to produce more white blood cells that help your body fight infection.

2. BEFORE YOU USE NEUPOPEG

Do not use Neupopeg

- if you are hypersensitive (allergic) to pegfilgrastim, filgrastim, *E. coli* derived proteins, or any of the other ingredients of Neupopeg.

Take special care with Neupopeg

Please tell your doctor:

- if you experience a cough, fever and difficulty breathing;
- if you have sickle cell anaemia;
- if you get left upper abdominal pain or pain at the tip of your shoulder.

- if you have an allergy to latex. The needle cover on the pre-filled syringe contains a derivative of latex and may cause severe allergic reactions.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine. Neupopeg has not been tested in pregnant women. It is important to tell your doctor if you:

- are pregnant;
- think you may be pregnant; or
- plan to become pregnant.

You must stop breast feeding if you use Neupopeg.

Driving and Using Machines

The effect of Neupopeg on the ability to drive or use machines is not known.

Important information about some of the ingredients of Neupopeg

Neupopeg contains sorbitol (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Neupopeg. Neupopeg is essentially sodium-free.

3. HOW TO USE NEUPOPEG

Neupopeg is for use in adults aged 18 and over.

Always take Neupopeg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. The usual dose is one 6 mg subcutaneous injection (injection under your skin) using a pre-filled syringe and it should be given approximately 24 hours after your last dose of chemotherapy at the end of each chemotherapy cycle.

Do not shake Neupopeg vigorously as this may affect its activity

Injecting Neupopeg yourself

Your doctor may decide that it would be more convenient for you to inject Neupopeg yourself. Your doctor or nurse will show you how to inject yourself. Do not try to inject yourself if you have not been trained.

For further instructions on how to inject yourself with Neupopeg, please read the section at the end of this leaflet.

If you use more Neupopeg than you should

If you use more Neupopeg than you should contact your doctor, nurse or pharmacist.

If you forget to inject Neupopeg

If you have forgotten a dose of Neupopeg, you should contact your doctor to discuss when you should inject the next dose.

4. POSSIBLE SIDE EFFECTS

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

A very common side effect (likely to occur in more than 1 in 10 patients) is bone pain. Your doctor will tell you what you can take to ease the bone pain.

Common side effects (likely to occur in fewer than 1 in 10 patients) include; pain and redness at the site of the injection, headaches, and general aches and pains in the joints, muscles, chest, limbs, neck or back. An uncommon side effect (likely to occur in fewer than 1 in 100 patients) is nausea.

Allergic-type reactions to Neupopeg, including redness and flushing, skin rash, raised areas of the skin that itch and anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face), have rarely (likely to occur in fewer than 1 in 1000 patients) been reported.

Increased spleen size and very rare cases (likely to occur in fewer than 1 in 10,000 patients)) of spleen rupture have been reported after the use of Neupopeg. Some cases of splenic rupture were fatal.

It is important that you contact your doctor immediately if you experience pain in the upper left side of the abdomen or left shoulder pain since this may relate to a problem with your spleen.

Rare (likely to occur in fewer than 1 in 1000 patients)cases of breathing problems have been reported after taking G-CSFs. If you have a cough, fever and difficulty breathing please tell your doctor.

Some changes may occur in your blood, but these will be detected by routine blood tests. Your platelet count may become low which might result in bruising. Your white blood cell count may become high for a short period of time.

Sweet's syndrome (plum-coloured, raised, painful lesions on the limbs and sometimes the face and neck with fever) has occurred very rarely (likely to occur in fewer than 1 in 1,000 patients) but other factors may play a role.

Very rarely (likely to occur in fewer than 1 in 10,000 patients) cutaneous vasculitis (inflammation of the blood vessels in the skin) has occurred in patients receiving Neupopeg.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPOPEG

Keep out of the reach and sight of children.

Do not use Neupopeg after the expiry date which is stated on the box and on the syringe label (EXP). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

You may take Neupopeg out of the refrigerator and keep it at room temperature (not above 30°C) for no longer than 3 days. Once a syringe has been removed from the refrigerator and has reached room temperature (not above 30°C) it must either be used within 3 days or disposed of.

Do not freeze. Neupopeg may be used if it is accidentally frozen for a single period of less than 24 hours.

Keep the container in the outer carton in order to protect from light.

Do not use Neupopeg if you notice it is cloudy or there are particles in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Neupopeg contains

Neupopeg contains the active substance pegfilgrastim. Pegfilgrastim is a protein produced by biotechnology in bacteria called *E. coli*. It belongs to a group of proteins called cytokines, and is very similar to a natural protein (granulocyte-colony stimulating factor) produced by your own body.

The active substance is pegfilgrastim. Each pre-filled syringe contains 6 mg of pegfilgrastim in 0.6 ml of solution.

The other ingredients are sodium acetate, sorbitol (E420), polysorbate 20 and water for injections.

What Neupopeg looks like and contents of the pack

Neupopeg is a solution for injection in a pre-filled syringe (6 mg/0.6 ml).

Each pack contains 1 pre-filled syringe. The syringes are provided either with or without a blister wrapping. It is a clear, colourless liquid.

Manufacturer:
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder:
Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

Further information

If you want more information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

This leaflet was last approved.

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

Instructions for injecting with the Neupopeg pre-filled syringe

This section contains information on how to give yourself an injection of Neupopeg. It is important that you do not try to give yourself the injection unless you have received training from your doctor, nurse, or pharmacist. If you have questions about how to inject, please ask your doctor, nurse, pharmacist for assistance.

How do you, or the person injecting you, use Neupopeg pre-filled syringe?

You will need to give yourself the injection into the tissue just under the skin. This is known as a subcutaneous injection.

Equipment that you need

To give yourself a subcutaneous injection you will need:

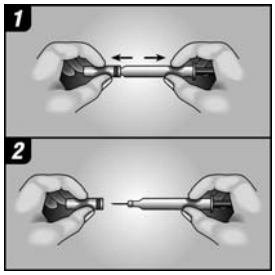
- a pre-filled syringe of Neupopeg; and
- alcohol wipes or similar.

What should I do before I give myself a subcutaneous injection of Neupopeg?

1. Remove from the refrigerator.
2. Do not shake the pre-filled syringe.
3. **Do not** remove the cover from the syringe until you are ready to inject.
4. Check the expiry date on the pre-filled syringe label (EXP). Do not use it if the date has passed the last day of the month shown.
5. Check the appearance of Neupopeg. It must be a clear and colourless liquid. If there are particles in it, you must not use it.
6. For a more comfortable injection, let the pre-filled syringe stand for 30 minutes to reach room temperature or hold the pre-filled syringe gently in your hand for a few minutes. **Do not** warm Neupopeg in any other way (for example, do not warm it in a microwave or in hot water).
7. **Wash your hands thoroughly**.
8. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

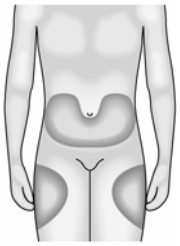
How do I prepare my Neupopeg injection?

Before you inject Neupopeg you must do the following:



1. Hold the syringe barrel and gently take the cover from the needle without twisting. Pull straight as shown in pictures 1 and 2. Do not touch the needle or push the plunger.
2. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
3. You can now use the pre-filled syringe.

Where should I give my injection?



The most suitable places to inject yourself are:

- the top of your thighs; and
- the abdomen, except for the area around the navel.

If someone else is injecting you, they can also use the back of your arms.

How do I give my injection?

1. Disinfect your skin by using an alcohol wipe and pinch the skin between your thumb and forefinger, without squeezing it.

2. Put the needle fully into the skin as shown by your nurse or doctor.

3. Pull slightly on the plunger to check that a blood vessel has not been punctured. If you see blood in the syringe, remove the needle and re-insert it in another place.

4. Inject the liquid slowly and evenly, always keeping your skin pinched.

5. After injecting the liquid, remove the needle and let go of your skin.

6. If you notice a spot of blood at the injection site dab away with a cotton ball or tissues. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

7. Only use each syringe for one injection. Do not use any Neupopeg that is left in the syringe.

Remember

If you have any problems, please do not be afraid to ask your doctor or nurse for help and advice.

Disposing of used syringes

- Do not put the cover back on used needles.

- Keep used syringes out of the reach and sight of children.

- The used syringe should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neupopeg 6 mg solution for injection in a pre-filled pen
pegfilgrastim

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. WHAT NEUPOPEG IS AND WHAT IT IS USED FOR

Neupopeg is used to reduce the duration of neutropenia (low white blood cell count) and the occurrence of febrile neutropenia (low white blood cell count with a fever) which can be caused by the use of cytotoxic chemotherapy (medicines that destroy rapidly growing cells). White blood cells are important as they help your body fight infection. These cells are very sensitive to the effects of chemotherapy which can cause the number of these cells in your body to decrease. If white blood cells fall to a low level there may not be enough left in the body to fight bacteria and you may have an increased risk of infection.

Your doctor has given you Neupopeg to encourage your bone marrow (part of the bone which makes blood cells) to produce more white blood cells that help your body fight infection.

2. BEFORE YOU USE NEUPOPEG

Do not use Neupopeg

- if you are hypersensitive (allergic) to pegfilgrastim, filgrastim, *E. coli* derived proteins, or any of the other ingredients of Neupopeg.

Take special care with Neupopeg

Please tell your doctor:

- if you experience a cough, fever and difficulty breathing;
- if you have sickle cell anaemia;
- if you get left upper abdominal pain or pain at the tip of your shoulder.

- if you have an allergy to latex. The needle cover on the pre-filled pen contains a derivative of latex and may cause severe allergic reactions.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine. Neupopeg has not been tested in pregnant women. It is important to tell your doctor if you:

- are pregnant;
- think you may be pregnant; or
- plan to become pregnant.

You must stop breast feeding if you use Neupopeg.

Driving and Using Machines

The effect of Neupopeg on the ability to drive or use machines is not known.

Important information about some of the ingredients of Neupopeg

Neupopeg contains sorbitol (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Neupopeg. Neupopeg is essentially sodium-free.

3. HOW TO USE NEUPOPEG

Neupopeg is for use in adults aged 18 and over.

Always take Neupopeg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. The usual dose is one 6 mg subcutaneous injection (injection under your skin) using a pre-filled syringe and it should be given approximately 24 hours after your last dose of chemotherapy at the end of each chemotherapy cycle.

Do not shake Neupopeg vigorously as this may affect its activity

Injecting Neupopeg yourself

Your doctor has decided it would be best for you to inject Neupopeg yourself. Your doctor or nurse will show you how to inject yourself. Do not try to inject yourself if you have not been trained.

For further instructions on how to inject yourself with Neupopeg, please read the section at the end of this leaflet.

If you use more Neupopeg than you should

If you use more Neupopeg than you should contact your doctor, nurse or pharmacist.

If you forget to inject Neupopeg

If you have forgotten a dose of Neupopeg, you should contact your doctor to discuss when you should inject the next dose.

4. POSSIBLE SIDE EFFECTS

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

A very common side effect (likely to occur in more than 1 in 10 patients) is bone pain. Your doctor will tell you what you can take to ease the bone pain.

Common side effects (likely to occur in fewer than 1 in 10 patients) include; pain and redness at the site of the injection, headaches, and general aches and pains in the joints, muscles, chest, limbs, neck or back. An uncommon side effect (likely to occur in fewer than 1 in 100 patients) is nausea.

Allergic-type reactions to Neupopeg, including redness and flushing, skin rash, raised areas of the skin that itch and anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face), have rarely (likely to occur in fewer than 1 in 1000 patients) been reported.

Increased spleen size and very rare cases (likely to occur in fewer than 1 in 10,000 patients)) of spleen rupture have been reported after the use of Neupopeg. Some cases of splenic rupture were fatal.

It is important that you contact your doctor immediately if you experience pain in the upper left side of the abdomen or left shoulder pain since this may relate to a problem with your spleen.

Rare (likely to occur in fewer than 1 in 1000 patients)cases of breathing problems have been reported after taking G-CSFs. If you have a cough, fever and difficulty breathing please tell your doctor.

Some changes may occur in your blood, but these will be detected by routine blood tests. Your platelet count may become low which might result in bruising. Your white blood cell count may become high for a short period of time.

Sweet's syndrome (plum-coloured, raised, painful lesions on the limbs and sometimes the face and neck with fever) has occurred very rarely (likely to occur in fewer than 1 in 10,000 patients) but other factors may play a role.

Very rarely (likely to occur in fewer than 1 in 10,000 patients) cutaneous vasculitis (inflammation of the blood vessels in the skin) has occurred in patients receiving Neupopeg.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NEUPOPEG

Keep out of the reach and sight of children.

Do not use Neupopeg after the expiry date which is stated on the box and on the pen label (EXP). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

You may take Neupopeg out of the refrigerator and keep it at room temperature (not above 30°C) for no longer than 3 days. Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (not above 30°C) it must either be used within 3 days or disposed of.

Do not freeze. Neupopeg may be used if it is accidentally frozen for a single period of less than 24 hours.

Keep the container in the outer carton in order to protect from light.

Do not use Neupopeg if you notice it is cloudy or there are particles in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

Neupopeg contains the active substance pegfilgrastim. Pegfilgrastim is a protein produced by biotechnology in bacteria called *E. coli*. It belongs to a group of proteins called cytokines, and is very similar to a natural protein (granulocyte-colony stimulating factor) produced by your own body.

What Neupopeg contains

The active substance is pegfilgrastim. Each pre-filled pen contains 6 mg of pegfilgrastim in 0.6 ml of solution.

The other ingredients are sodium acetate, sorbitol (E420), polysorbate 20 and water for injections.

What Neupopeg looks like and contents of the pack

Neupopeg is a solution for injection in a pre-filled pen (6 mg/0.6 ml).

Each pack contains 1 pre-filled pen. It is a clear, colourless liquid.

Manufacturer:
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder:
Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

Further information

If you want more information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

This leaflet was last approved.

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

Instructions for injecting with the Neupopeg pre-filled pen (SureClick)

This section contains information on how to properly use the Neupopeg pre-filled pen. It is important that you do not try to give yourself the injection unless you have received training from your doctor, nurse, or pharmacist. If you have questions about how to inject, please ask your doctor, nurse, pharmacist for assistance.

How do you, or the person injecting you, use Neupopeg pre-filled pen (SureClick)?

You will need to give yourself the injection into the tissue just under the skin. This is called a subcutaneous injection.

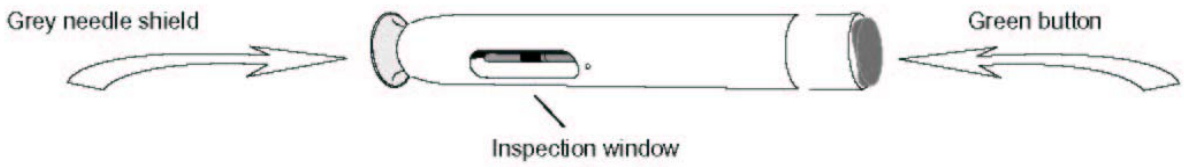
Equipment:

To give yourself a subcutaneous injection you will need:

- a new Neupopeg pre-filled pen and
- alcohol wipes or similar.

Preparing for a Neupopeg injection?

1. Remove from the refrigerator.
2. Do not shake the pre-filled pen.
3. **Do not** remove the grey needle shield from the pre-filled pen until you are ready to inject.
4. Check the expiry date on the pre-filled pen label (EXP:). Do not use it if the date has passed the last day of the month shown
5. Check the appearance of Neupopeg through the inspection window. It must be a clear and colourless liquid. If there are particles in it, you must not use it.
6. For a more comfortable injection, leave at room temperature for approximately 30 minutes. **Do not** warm Neupopeg in any other way (for example, do not warm it in a microwave or in hot water).
7. **Wash your hands thoroughly**.
8. Find a comfortable, well-lit, clean place and put all the equipment you need within reach.



Before use (with grey needle shield)

Before use (without grey needle shield)

After use (needle safety cover down)

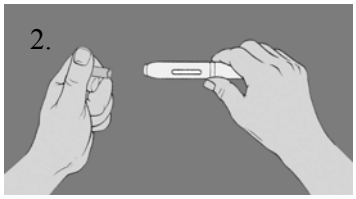
Where should I give my injection?

To perform a successful injection a firm injection area is required.

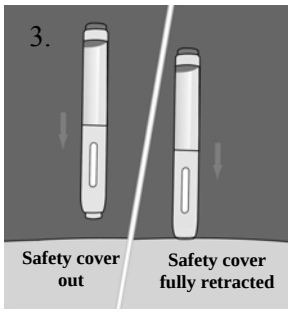
The recommended sites for injection using the pre-filled pen are the top of the thigh and the back of the arm if given by a nurse or carer (see picture 1).

The abdomen can be considered when the thigh and back of arm are judged by a healthcare professional to be inappropriate.

How to give an injection into the thigh or back of the arm

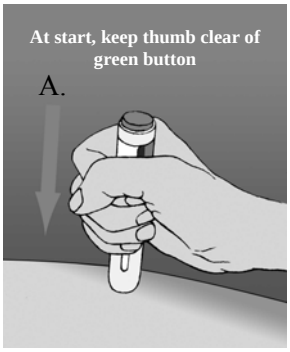


- Disinfect your skin by using an alcohol wipe.
- Remove the grey needle shield (see picture 2).



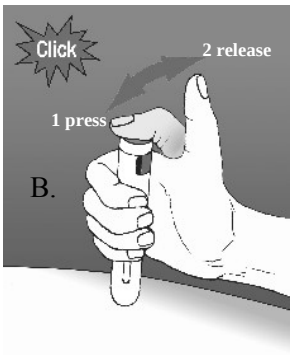
- The pre-filled pen has a safety cover that will protect you from needle sticks or loss of medicine by accidental bumping or touching.

Important information for Step A of the injecting process.
Press the pre-filled pen firmly enough against the skin so that the safety cover is fully retracted (see picture 3).

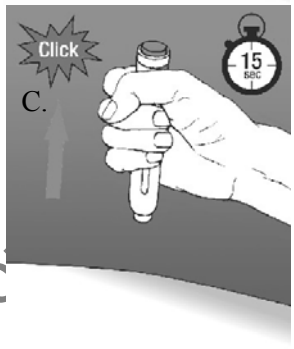


A. Place the pre-filled pen on the injection site at a right angle (90 degrees) and push firmly against the skin. **Hold down** (see picture).

B. While holding the pre-filled pen in place, (1) press and (2) release the green button on top. You will hear a "click". **Do not lift the pre-filled pen.**



C. **After the second "click"** (or count of 15) lift pre-filled pen from the injection site.



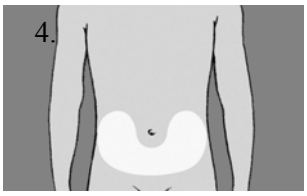
<u>If you experience difficulties choose a more firm injection site.</u>

The needle safety cover will move down over the needle and lock into place. The inspection window will be green, confirming the injection is complete.

If you notice a spot of blood at the injection site dab away with a cotton ball or tissues. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

Only use a single Neupopeg pre-filled pen for each injection.

How to inject into the abdomen

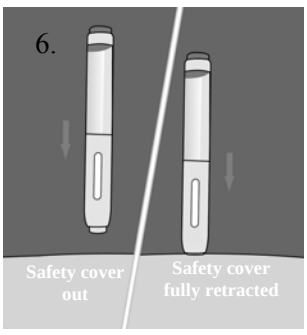


Important skin pinch technique

The objective of the skin pinch technique is to create a firm site for the injection

Choose a site at least 5 cm away from the belly button (navel) (see picture 4).

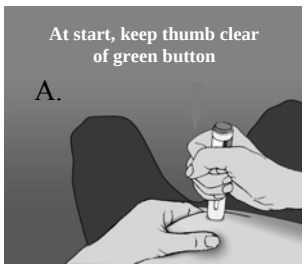
Pinch the skin of the abdomen **firmly** between the thumb and fingers creating a space at least 3 cm wide (twice the width of the tip of the pre-filled pen). Maintain firm skin pinch for entire procedure (see picture 5).



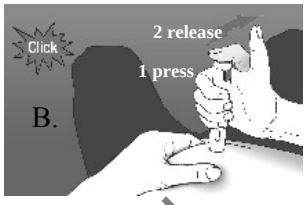
Important information for Step A of the injecting process.
Press the pre-filled pen firmly enough against the skin so that the safety cover is fully retracted (see picture 6).

The pre-filled pen has a safety cover that will protect you from needle sticks or loss of drug by accidental bumping or touching.

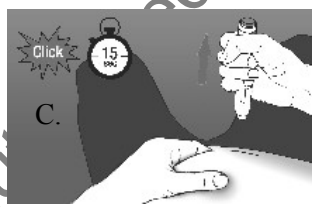
A. Centre the pre-filled pen in the area of the pinched skin at a right angle (90 degrees) and push firmly against the skin. **Hold down.**



B. Maintaining firm skin pinch, (1) press and (2) release the green button on top. You will hear a "click". **Do not lift the pre-filled pen**.



C. **After the second "click"** (or a count of 15) lift the pre-filled pen from the injection site**.**



<u>If you experience difficulties choose a more firm injection site.</u>

The needle safety cover will move down over the needle and lock into place. The inspection window will be green, confirming the injection is complete.

If you notice a spot of blood at the injection site dab away with a cotton ball or tissues. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

Only use a single Neupopeg pre-filled pen for each injection.

Remember

If you have any problems, please do not be afraid to ask your doctor or nurse for help and advice.

Disposing of used pre-filled pens

- Due to the protective safety cover it is not recommended to put the grey needle shield back on the used pre-filled pen.
- Keep used pens out of the reach and sight of children.
- The used pre-filled pen should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment