ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Neulasta 6 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

6 mg of pegfilgrastim in 0.6 ml (10 mg/ml*) solution for injection.

Pegfilgrastim is produced by r-DNA technology in *E. coli* (K12).

For excipients, see 6.1.

* Based on protein only. The concentration is 20 mg/ml if the PEG moiety is included.

3. PHARMACEUTICAL FORM

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

One 6 mg dose (a single pre-filled syringe) of Neulasta is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy. There are insufficient data to recommend the use of Neulasta in children and adolescents under 18 years of age.

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

4.3 Contraindications

Hypersensitivity to pegfilgrastim, filgrastim, *E. coli* derived proteins, or to any excipients.

4.4 Special warnings and special precautions for use

The safety and efficacy of Neulasta have not been investigated in patients with acute leukaemia and should not be used in such patients receiving myelosuppressive chemotherapy.

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

Rare (>0.01% and <0.1%) pulmonary adverse effects, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function 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.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported in healthy donors and patients following administration of granulocyte-colony stimulating factors (GCSFs). Some cases of splenic rupture were fatal. Therefore, spleen size should be carefully monitored (eg clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Treatment with Neulasta 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.

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

Publications have reported that high leucocyte counts are disadvantageous prognostic factors in patients with sickle-cell anaemia. Therefore, physicians should exercise caution when administering Neulasta in patients with sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of Neulasta with splenic enlargement and vaso-occlusive crisis.

White blood cell counts of $100 \times 10^9 /l$ or greater have been observed in less than 1% of patients receiving Neulasta. No adverse events directly attributable to this degree of leucocytosis 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 Neulasta.

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

4.5 Interactions with other medicinal products and other forms of interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Neulasta should be administered approximately 24 hours after administration of cytotoxic chemotherapy. In clinical studies, Neulasta has been safely administered 14 days before chemotherapy. Concomitant use of Neulasta with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of Neulasta 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 Neulasta have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression eg, nitrosoureas.

Specific interaction or metabolism studies have not been performed, however, clinical studies have not indicated an interaction of Neulasta 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.
Neulasta should not be used during pregnancy unless clearly necessary.

There is no clinical experience with lactating women, therefore Neulasta 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 Neulasta 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 and hypotension, occurring on initial or subsequent treatment have been reported both with Neulasta and with the parent compound of Neulasta, filgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship.

Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, were common; reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were very common in patients receiving Neulasta following cytotoxic chemotherapy. Nausea was observed in healthy volunteers and patients receiving chemotherapy.

Common but generally asymptomatic cases of splenomegaly and very rare cases of splenic rupture have been reported in healthy donors and patients following administration of granulocyte-colony stimulating factors (G-CSFs) (see Section 4.4).

Rare 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 4.4).

Rare cases of thrombocytopenia and leukocytosis have been reported.

Very rare cases of Sweet’s syndrome have been reported, although in some cases underlying haematological malignancies may play a role.

Very common (≥ 10%) and common (≥ 1%, < 10%) undesirable effects in clinical studies were:

<table>
<thead>
<tr>
<th>Body system</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculo skeletal</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Skeletal pain</td>
</tr>
<tr>
<td>Application site</td>
<td>Common</td>
</tr>
<tr>
<td>Body as a whole</td>
<td>Injection site pain</td>
</tr>
<tr>
<td>CNS/PNS</td>
<td>Chest pain (non-cardiac), pain</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Arthralgia, myalgia, and back, limb, musculo-skeletal, and neck pain</td>
</tr>
</tbody>
</table>

4.9 Overdose

There is no experience with overdose of Neulasta 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 to 7 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 mcg/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 100mg/m² 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)

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).
Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment.

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 leucocyte 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

Neulasta is incompatible with sodium chloride solutions.

6.3 Shelf life

30 months.
6.4 Special precautions for storage

Store at 2°C – 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 the container in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Single use Type I glass pre-filled syringe with a stainless steel needle.

Each carton contains 1 pre-filled syringe. The syringes may be presented in either blistered or non-blistered packaging.

Not all packs may be marketed.

6.6 Instructions for use, handling and disposal

Neulasta is a sterile but unpreserved solution.

Before administration, Neulasta solution should be inspected for visible particles. 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

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/227/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

22 August 2002

10. DATE OF REVISION OF THE TEXT
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 AUTHORIZATION 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 AUTHORIZATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORIZATION HOLDER

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

• OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
1. **NAME OF THE MEDICINAL PRODUCT**

Neulasta 6 mg  
Solution for injection  
Pegfilgrastim

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pre-filled syringe contains 6 mg pegfilgrastim (10 mg/ml).

3. **LIST OF EXCIPIENTS**

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

4. **PHARMACEUTICAL FORM AND CONTENTS**

1 single use pre-filled syringe  
0.6 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For subcutaneous 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.  
Before use, read package leaflet carefully.

8. **EXPIRY DATE**

EXP.:

9. **SPECIAL STORAGE CONDITIONS**

Store at 2°C – 8°C (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

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/227/001

## 13. MANUFACTURER'S BATCH NUMBER

LOT:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
### BLISTER PACK WITH SYRINGE

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Neulasta 6 mg injection Pegfilgrastim</td>
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<table>
<thead>
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<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tr>
<td>Amgen Europe B.V.</td>
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<th>3. EXPIRY DATE</th>
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<td>EXP.:</td>
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<th>4. BATCH NUMBER</th>
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<td>LOT:</td>
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</table>

### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
### BLISTERED SYRINGE LABEL

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neulasta 6 mg Pegfilgrastim</td>
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<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<td>SC</td>
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<th>3. EXPIRY DATE</th>
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<th>4. BATCH NUMBER</th>
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<td>LOT:</td>
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<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6 ml</td>
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<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen Europe B.V.</td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING UNBLISTERED SYRINGE OUTER CARTON</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Neulasta 6 mg</td>
</tr>
<tr>
<td>Solution for injection</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
</tr>
<tr>
<td><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></td>
</tr>
<tr>
<td>Each pre-filled syringe contains 6 mg pegfilgrastim (10 mg/ml).</td>
</tr>
<tr>
<td><strong>3. LIST OF EXCIPIENTS</strong></td>
</tr>
<tr>
<td>Excipients: sodium acetate, sorbitol (E420), polysorbate 20, water for injections.</td>
</tr>
<tr>
<td><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></td>
</tr>
<tr>
<td>1 single use pre-filled syringe</td>
</tr>
<tr>
<td>0.6 ml</td>
</tr>
<tr>
<td><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
<tr>
<td>For subcutaneous use</td>
</tr>
<tr>
<td><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></td>
</tr>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
<tr>
<td><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></td>
</tr>
<tr>
<td>Avoid vigorous shaking.</td>
</tr>
<tr>
<td>Before use, read package leaflet carefully.</td>
</tr>
<tr>
<td><strong>8. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP.:</td>
</tr>
<tr>
<td><strong>9. SPECIAL STORAGE CONDITIONS</strong></td>
</tr>
<tr>
<td>Store at 2°C – 8°C (in a refrigerator).</td>
</tr>
<tr>
<td>Do not freeze.</td>
</tr>
<tr>
<td>Keep the container in the outer carton, in order to protect from light.</td>
</tr>
<tr>
<td><strong>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></td>
</tr>
<tr>
<td>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
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<td>----------------------------------------------------------</td>
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<tr>
<td>Amgen Europe B.V.</td>
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<tr>
<td>Minervum 7061</td>
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<tr>
<td>4817 ZK Breda</td>
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<tr>
<td>The Netherlands</td>
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<table>
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<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<td>EU/1/02/227/002</td>
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<tr>
<th>13. MANUFACTURER'S BATCH NUMBER</th>
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<td>LOT:</td>
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<table>
<thead>
<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
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</thead>
<tbody>
<tr>
<td>Medicinal product subject to medical prescription.</td>
</tr>
</tbody>
</table>

| 15. INSTRUCTIONS ON USE                                   |

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED SYRINGE LABEL**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neulasta 6 mg</td>
</tr>
<tr>
<td>injection</td>
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<tr>
<td>Pegfilgrastim</td>
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<table>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<td>SC</td>
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<th>3. EXPIRY DATE</th>
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<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tbody>
<tr>
<td>0.6 ml</td>
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<tr>
<th>6. OTHER</th>
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<tr>
<td>Amgen Europe B.V.</td>
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</table>
B. PACKAGE LEAFLET
PACKAGE LEAFLET

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 personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet

1. What Neulasta is and what it is used for
2. Before you use Neulasta
3. How to use Neulasta
4. Possible side effects
5. Storing Neulasta
6. Information for injecting yourself

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

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.

Marketing Authorisation Holder and Manufacturer:

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

1. WHAT NEULASTA IS AND WHAT IT IS USED FOR

Neulasta is a solution for injection in a pre-filled syringe. Each pack contains 1 pre-filled syringe. The syringes are provided either with or without a blister wrapping. Neulasta is a clear, colourless solution.

Neulasta 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.

Neulasta 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 Neulasta 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 NEULASTA

Neulasta is for use in adults aged 18 and over.

Do not use Neulasta

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

Please tell your doctor

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

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine. Neulasta 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 Neulasta.

Driving and Using Machines

The effect of Neulasta on the ability to drive or use machinery is not known.

Using other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO USE NEULASTA

Always take Neulasta 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.

Injecting Neulasta yourself

Your doctor may decide that it would be more convenient for you to inject Neulasta 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 Neulasta, please read section 6 at the end of this leaflet.
If you use more Neulasta than you should

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

If you forget to inject Neulasta

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Neulasta can have side effects.

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

Common side effects (more than 1%, less than 10%) include; pain 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 (more than 0.1%, less than 1%) is nausea.

Allergic-type reactions to Neulasta, including skin rash, raised areas of the skin that itch and anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face), have rarely been reported.

Increased spleen size and very rare cases (less than 0.01%) of spleen rupture have been reported in stem cell donors taking G-CSFs and in patients. 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 (more than 0.01% but less than 0.1%) 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 (less than 0.01%) but other factors may play a role.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING NEULASTA

Keep out of the reach and sight of children.

Store at 2°C – 8°C (in a refrigerator).

You may take Neulasta 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. Neulasta 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.
The expiry date for Neulasta is printed on the box and on the syringe label. Do not use Neulasta after this date, the last day of the month shown.

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

Do not shake Neulasta vigorously as this may affect its activity.

6. INFORMATION FOR INJECTING YOURSELF

This section contains information on how to give yourself an injection of Neulasta. It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. It is also important that you dispose of the syringe in a puncture-proof container. If you are not sure about giving yourself the injection or you have any questions, please ask your doctor or nurse for help.

How do I inject Neulasta myself?

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 Neulasta;

• alcohol wipes or similar; and

• a puncture-proof container (plastic container provided by the hospital or pharmacy) so you can dispose of used syringes safely.

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

1. Take your Neulasta pre-filled syringe out of the refrigerator.

2. Do not shake the pre-filled syringe.

3. 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.

4. Check the appearance of Neulasta. It must be a clear and colourless liquid. If there are particles in it, you must not use it.

5. 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 Neulasta in any other way (for example, do not warm it in a microwave or in hot water).

6. Do not remove the cover from the syringe until you are ready to inject.

7. Wash your hands thoroughly.

8. Find a comfortable, well-lit place and put everything you need where you can reach it (the Neulasta pre-filled syringe, alcohol wipes and the puncture-proof container).

How do I prepare my Neulasta injection?
Before you inject Neulasta 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. Only use each syringe for one injection. Do not use any Neulasta 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.

- Put used syringes into the puncture-proof container and keep it out of the reach and sight of children.

- Dispose of the full puncture-proof container as instructed by your doctor, nurse or pharmacist.

- Never put the syringes that you have used into your normal household rubbish bin.

Further information

If you want more information about this medicine, please contact the local representative of the Marketing Authorisation Holder.
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This leaflet was last approved on