

**ANNEX I**

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE  
SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA**

## SCIENTIFIC CONCLUSIONS

The CPMP, having considered the points of disagreement and the responses provided by the Marketing Authorisation Holders as set out in the appended variation arbitration assessment report, is of the opinion that the objections raised by Germany should not prevent the approval of the variations applied for.

The summary of product characteristics was amended in order to define clearly the indications, to highlight the contraindication to the concomitant use of the product with radiotherapy, and to clarify the text regarding the risk and the precautions to be taken regarding thrombocytopenia. A short description of the clinical trials for the two indications was also included.

On the basis of the available data the CPMP considered that the risk-benefit assessment for Leucomax is in favour of the product for the following indications:

- Reduction of the risk of infection due to neutropenia in patients treated with cytotoxic chemotherapy for malignant diseases
- Reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by autologous bone marrow transplantation (BMT), in patients considered to be at increased risk of prolonged severe neutropenia and in patients with evidence of graft failure.

the CPMP has recommended the amendment of the Summary of Product Characteristics and the granting of the variation of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III for Leucomax/Mielogen/SCH39300 (see Annex II).

Leucomax is a medicinal product administered under the supervision of experienced physicians. The summary of product characteristics of Leucomax was reviewed in order to better reflect the state of the knowledge. Amendments to the SPC were agreed in order to define more clearly the indications, to highlight the reasons for the contraindication to the concomitant use of the product with radiotherapy and to include the relevant precautions for the risk of thrombocytopenia. Furthermore description of relevant results of major randomised controlled clinical trials were included in section 5.1 Pharmacodynamic Properties.

## OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF Leucomax/Mielogen /SCH39300 (see Annex II)

The data available demonstrate that the product reduces the duration of neutropenia following myeloablation and autologous BMT; a time when patients are at very significant risk of contracting bacterial infections. The safety profile is well described and appears acceptable.

### *Clinical efficacy / Safety*

It appears that administration of GM-CSF after chemotherapy can reduce the risk of infection due to the myelotoxicity of the antineoplastic regimen administered; however, the dose intensity of the regimen is not affected by the administration of GM-CSF. The hope of a decade ago, that administration of colony stimulating factors will improve the outcome of patients treated with (radio-)

chemotherapy for malignant disease by means of overcoming the dose limiting toxicity neutropenia of those regimens, has to be considered as disappointed from a today's point of view. There is no convincing evidence that administration of Leucomax can improve outcome of patients with malignant diseases in terms of overall survival or tumour response by means of an increased dose intensity.

In using GM-CSF in the chemotherapy setting a consistent shortening of the duration of neutropenia and decrease in infections was seen.

The CPMP "Note for Guidance on clinical trials with haematopoietic factors for the prophylaxis of infection following myeloablative therapy" (CPMP/EWP/555/95) clearly indicates that the primary objective for the registration of phase III trials of haematopoietic growth factors should be the reduction of the frequency of infections. In the evaluation of Leucomax infection was defined using an algorithm prospectively derived by the German Lymphoma Cooperative Group. The grade of the severity was based on several factors including use of oral antibiotics, the number and duration of antibiotics and the duration of fever. Reduction in the risk of developing an infection translated into a significant decrease in the use and duration of iv antibiotics was seen in the clinical trials in the GM-CSF group vs the non- GM-CSF group. The duration of antibiotic therapy was also shorter. These results translated a reduction in the proportion of patients hospitalised and in the shortening in the duration of hospitalisation.

Several clinical trials with GM-CSFs in general (and molgramostim in particular) indicate that benefit and risk of treatment with molgramostim in the context of myelotoxic therapy depend on several, not fully identified factors such as e.g. timing of molgramostim treatment in relation to, and intensity of the myelotoxic therapy administered:

In a randomized, double blind trial (CSF-B301) with 172 high grade non-Hodgkin's Lymphoma patients treated with COP-BLAM administration of GM-CSF reduced the risk of infection. Also a small increase of dose intensity of COP-BLAM was observed which was not translated into increased survival.

In a randomized, open label trial using sargramostim (Bunn et al) administering VP-16 and cisplatin from day 1 to 3 of a cycle (one cycle represents 18 days; overall 6 cycles), and wide field chest irradiation on 5 days of each week, to 230 patients with limited SCLC the following results were observed for GM-CSF (in comparison with no GM-CSF treatment): Higher neutrophil counts, more grade III to IV thrombocytopenias (in particular during cycle 2), and more toxic deaths. In addition, unfavorable trends in terms of increased i.v. antibiotic usage, decreased complete response rate and impaired survival were also present. GM-CSF administration had no apparent effect on dose intensity of the radiotherapy administered but the chemotherapy dose delivered was smaller in the GM-CSF arm. The unfavourable short term outcome of patients in the GM-CSF arm was explained by the partially overlapping administration of radiotherapy with GM-CSF, i.e. concomitant use of GM-CSF and wide field chest irradiation. Leucomax is contraindicated for concomitant use with wide field radiotherapy, the background reasons for this contraindications are now provided in the SPC.

In a randomized trial in 408 patients treated with GM-CSF or placebo after myeloablative therapy (predominantly for non-Hodgkin's Lymphoma and Hodgkin's disease) followed by autologous bone marrow or peripheral stem cell transplantation a strong effect of GM-CSF in terms of a shortened duration of neutropenia was observed. In addition to this result, no relevant differences in outcome for GM-CSF and placebo, in particular in terms of risk of infection, can be described.

The CPMP convened an ad-hoc experts meeting. An oral presentation was given by the MAHs.

In order to evaluate whether there are any signals deriving from the trials CSF-B301 and Bunn et al, the experts group discussed whether the MAHs for Leucomax should commit to conduct a meta-analysis of all carried out randomised controlled clinical trials investigating post-chemotherapy administration of GM-CSF vs. no GM-CSF in patients with malignant diseases. Methodological details of this meta-analysis were discussed among the experts group, and also with the MAHs.

The ad-hoc Experts meeting concluded that a meta-analysis would not be useful as it would not add to the information available. Because of the nature of these trials, a meta-analysis

would combine very heterogeneous trials with important differences in underlying disease, therapies and patient selection, making the overall result hard to interpret.

Additional clinical studies were considered neither feasible nor necessary. The group proposed amendments to the summary of product characteristics in order to define clearly the indications, to highlight the contraindication to the concomitant use of the product with radiotherapy and include the relevant precautions for the risk of thrombocytopenia.

## Amendments to the Summary of Product Characteristics

### 4.1 Therapeutic indications

LEUCOMAX / MIELOGEN / SCH39300 is indicated to reduce the risk of infection due to neutropenia in patients treated with cytotoxic chemotherapy for malignant diseases (see section 4.4, Special precautions for use, Laboratory tests). This risk of infection due to neutropenia, and therefore the clinical benefit of LEUCOMAX / MIELOGEN / SCH39300 treatment, depends on the intensity of the cytotoxic chemotherapy administered.

LEUCOMAX / MIELOGEN / SCH39300 is indicated for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by autologous bone marrow transplantation (BMT), in patients considered to be at increased risk of prolonged severe neutropenia and in patients with evidence of graft failure.

There is insufficient clinical trial data on the use of LEUCOMAX / MIELOGEN / SCH39300 after allogeneic BMT or after peripheral blood stem cells (PBSC) transplantation to recommend its use.

### 4.3 Contraindications

LEUCOMAX / MIELOGEN / SCH39300 is contraindicated:

- in patients with a history of hypersensitivity to molgramostim or any component of the injectable formulation.
- for concomitant use with wide field radiotherapy as patients treated with GM-CSF had increased incidence of pulmonary adverse events, including fatalities.
- for the purpose of increasing the dose intensity of cytotoxic chemotherapy beyond established dosage regimens.

### 4.4 Special warnings and special precautions for use

#### Special precautions for use

Patients receiving LEUCOMAX / MIELOGEN / SCH39300 are at greater risk of thrombocytopenia. Regular monitoring of the platelet count and haematocrit is recommended.

**Laboratory tests** – Standard haematological tests (complete blood count, and differential and platelet count) should be performed and serum albumin levels monitored during therapy with LEUCOMAX / MIELOGEN / SCH39300.

### 5.1 Pharmacodynamic properties

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

#### Effects observed in clinical trials in chemotherapy setting

In a randomized, double-blind trial with 172 high-grade non-Hodgkin's Lymphoma patients treated with COP-BLAM, administration of GM-CSF reduced the risk of infection. Also, a small increase in dose intensity of COP-BLAM was observed which was not translated into increased survival.

#### Effects observed in clinical trials in autologous bone marrow transplantation setting

In a randomized trial in 408 patients treated with GM-CSF or placebo after myeloablative

therapy (predominantly for non-Hodgkin's Lymphoma and Hodgkin's disease) followed by autologous bone marrow or peripheral stem cell transplantation, patients in the GM-CSF arm showed a shortened duration of neutropenia. However, relevant differences in outcome for GM-CSF and placebo, in particular in terms of risk of infection, have not been demonstrated.

## **ANNEX II**

### **LIST OF THE NAME, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, APPLICANTS MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES**

**ANNEX II**

| <b><u>Member State</u></b> | <b><u>Marketing Authorisation Holder</u></b>   | <b><u>Tradename Name</u></b> | <b><u>Strength</u></b> | <b><u>Pharmaceutical Form</u></b>             | <b><u>Packaging</u></b>                        | <b><u>Package-size</u></b>   | <b><u>Route of administration</u></b> |
|----------------------------|--|------------------------------|------------------------|---|--|--|---------------------------------------|
| Austria                    | Novartis Pharma GmbH<br>Brunnerstrasse 59,<br>A-1235 Wien AUSTRIA  | 1. Leucomax<br>"Novartis"    | 150 mcg                | Powder and solvent for solution for injection | Glass vial (Powder)<br>Glass ampoule (Solvent) | 1 vial and 1 ampoule per pack (all strengths)<br>5 vials and 5 ampoules per pack (all strengths) | Intravenous<br>Subcutaneous           |
|                            |  |                              | 300 mcg                |   |  |  |                                       |
|                            | AESCA Chemisch-Pharmazeutische Fabrik GmbH<br>Badener Strasse 23,<br>A-2514 Traiskirchen AUSTRIA   | 2. Leucomax<br>"AESCA"       | 150 mcg                | Powder and solvent for solution for injection |  |  |                                       |
|                            |  |                              | 300 mcg                |   |  |  |                                       |
|                            |  |                              | 400 mcg                |   |  |  |                                       |
| Belgium                    | Novartis Pharma SA<br>Chaussée de Haecht 226,<br>B-1030 Bruxelles BELGIUM  | Leucomax                     | 150 mcg                | Powder and solvent for solution for injection | Glass vial (Powder)<br>Glass ampoule (Solvent) | 1 vial and 1 ampoule per pack (all strengths)<br>5 vials and 5 ampoules per pack (all strengths) | Intravenous<br>Subcutaneous           |
|                            |  |                              | 300 mcg                |   |  |  |                                       |
|                            |  |                              | 400 mcg                |   |  |  |                                       |
| Denmark                    | <u>The MAH is held jointly by</u><br>Novartis Healthcare A/S<br>Lyngbyvej 172, DK-2100<br>Copenhagen,<br>DENMARK<br><u>and</u><br>Schering-Plough A/S<br>Hvedemarken 12, DK-<br>3520 Farum DENMARK | Leucomax                     | 150 mcg                | Powder and solvent for solution for injection | Glass vial (Powder)<br>Glass ampoule (Solvent) | 1 vial and 1 ampoule per pack (all strengths)  | Intravenous<br>Subcutaneous           |
|                            |  |                              | 300 mcg                |   |  |  |                                       |
|                            |  |                              | 400 mcg                |   |  |  |                                       |
| Finland                    | Schering-Plough (Brinny) Company<br>Innishannon  | Leucomax                     | 150 mcg                | Powder and solvent for solution for           | Glass vial (Powder)<br>Glass                   | 1 vial and 1 ampoule per pack (all strengths)  | Intravenous<br>Subcutaneous           |
|                            |  |                              | 300 mcg                |   |  |  |                                       |
|                            |  |                              | 400 mcg                |   |  |  |                                       |

County Cork IRELAND

injection

ampoule  
(Solvent)

| <u>Member State</u> | <u>Marketing Authorisation Holder</u>   | <u>Tradename Name</u>   | <u>Strength</u>                         | <u>Pharmaceutical Form</u>                             | <u>Packaging</u>  | <u>Package Size</u>  | <u>Route of Administration</u> |
|---------------------|---|---|---|--|---|--|--------------------------------|
| France              | The MAH is held jointly by<br>Laboratoires NOVARTIS<br>2 et 4, rue Lionel Terray<br>92506, Rueil Malmaison<br>FRANCE<br><u>and</u><br>Schering-Plough<br>92, rue Baudin<br>92307 Levallois-Perret<br>Cedex FRANCE | Leucomax  | 50 mcg<br>150 mcg<br>300 mcg<br>400 mcg | Powder and<br>solvent for<br>solution for<br>injection | Glass vial<br>(Powder)<br>Glass<br>ampoule<br>(Solvent) | 1 vial and 1 ampoule<br>per pack (all<br>strengths)<br>+ 2 needles per pack  | Intravenous<br>Subcutaneous    |
| Germany             | Novartis Pharma GmbH<br>Roonstrasse 25,<br>D-90429 Nürnberg<br>GERMANY  | (1) Leucomax  | 150 mcg<br>300 mcg<br>400 mcg           | Powder and<br>solvent for<br>solution for<br>injection | Glass vial<br>(Powder)<br>Glass<br>ampoule<br>(Solvent) | 1 vial and 1 ampoule<br>per pack (all<br>strengths)<br>5 vials and 5<br>ampoules per pack<br>(all strengths)<br>(300 + 400 mcg<br>strengths) | Intravenous<br>Subcutaneous    |
|                     | Essex Pharma GmbH<br>Thomas-Dehler-Strasse 27,<br>D-81737 München<br>GERMANY  | (2*) SCH39300/15<br>SCH39300/300<br>SCH39300/400<br><small>* Not marketed</small> | 150 mcg<br>300 mcg<br>400 mcg           | Powder and<br>solvent for<br>solution for<br>injection |   |  |                                |
| Greece              | Novartis [Hellas] S.A.C.I.<br>12Klm National Road No.1<br>GR-14451 Athens<br>GREECE   | (1) Leucomax  | 150 mcg<br>300 mcg<br>400 mcg           | Powder and<br>solvent for<br>solution for<br>injection | Glass vial<br>(Powder)<br>Glass<br>ampoule<br>(Solvent) | 1 vial and 1 ampoule<br>per pack (all<br>strengths)  | Intravenous<br>Subcutaneous    |
|                     |   | (2) Mielogen  | 150 mcg                                 |  |   |  |                                |



Schering-Plough S.A.  
AG. Dimitriou 63  
GR-17455 Alimos  
GREECE

300 mcg Powder and  
400 mcg solvent for  
solution for  
injection

| <u>Member State</u> | <u>Marketing Authorisation Holder</u>  | <u>Tradename</u> | <u>Strength</u>               | <u>Pharmaceutical Form</u>                             | <u>Packaging</u>  | <u>Package Size</u>  | <u>Route of Administration</u> |
|---------------------|--|------------------|-------------------------------|--|---|--|--------------------------------|
| Ireland             | Schering-Plough Ltd<br>Shire Park,<br>Welwyn Garden City,<br>Hertfordshire, AL7 1TW,<br>UK | Leucomax         | 150 mcg<br>300 mcg<br>400 mcg | Powder and<br>solvent for<br>solution for<br>injection | Glass vial<br>(Powder)<br>Glass<br>ampoule<br>(Solvent) | 1 vial and 1 ampoule<br>per pack (all<br>strengths)  | Intravenous<br>Subcutaneous    |
| Italy               | Novartis Farma S.p.A.<br>S.S. 233 (Varesina),<br>Km 20,5<br>21040 Origgio (VA)<br>ITALY    | (1) Leucomax     | 150 mcg<br>300 mcg<br>400 mcg | Powder and<br>solvent for<br>solution for<br>injection | Glass vial<br>(Powder)<br>Glass<br>ampoule<br>(Solvent) | 1 vial and 1 ampoule<br>per pack (all<br>strengths)<br>3 vials and 3<br>ampoules per pack<br>(all strengths) | Intravenous<br>Subcutaneous    |
|                     | Schering-Plough S.p.A.<br>Via Ripamonti, 89<br>20141 Milano ITALY                          | (2) Mielogen     | 150 mcg<br>300 mcg<br>400 mcg | Powder and<br>solvent for<br>solution for<br>injection |   | (150 + 300 mcg<br>strengths)   |                                |
| Luxembur<br>g       | Novartis Pharma GmbH<br>Roonstrasse 25<br>D-90429 Nürnberg<br>GERMANY                      | Leucomax         | 150 mcg<br>300 mcg<br>400 mcg | Powder and<br>solvent for<br>solution for<br>injection | Glass vial<br>(Powder)<br>Glass<br>ampoule<br>(Solvent) | 1 vial and 1 ampoule<br>per pack (all<br>strengths)<br>(300 + 400 mcg<br>strengths)                          | Intravenous<br>Subcutaneous    |

|                            |   |                              |                               |   |  |   |                                       |
|----------------------------|---|------------------------------|-------------------------------|---|--|---|---------------------------------------|
| Netherlands                | Novartis Pharma B.V.<br>Raapopseweg 1<br>Postbus 241<br>6800 LZ Arnhem<br>The NETHERLANDS   | Leucomax                     | 150 mcg<br>300 mcg<br>400 mcg | Powder and solvent for solution for injection | Glass vial (Powder)<br>Glass ampoule (Solvent) | 1 vial and 1 ampoule per pack (all strengths) | Intravenous<br>Subcutaneous           |
| Portugal                   | Novartis Farma - Produtos Farmacêuticos SA<br>Estrada dos Casais, Alto do Forte,<br>2735 Rio de Mouro<br>PORTUGAL                                       | Leucomax                     | 150 mcg<br>300 mcg<br>400 mcg | Powder and solvent for solution for injection | Glass vial (Powder)<br>Glass ampoule (Solvent) | 1 vial and 1 ampoule per pack (all strengths) | Intravenous<br>Subcutaneous           |
| Spain                      | Novartis Farmacéutica, S.A.<br>Gran Via de les Corts Catalanes, 764,<br>08013-Barcelona SPAIN   | Leucomax                     | 150 mcg<br>300 mcg<br>400 mcg | Powder and solvent for solution for injection | Glass vial (Powder)<br>Glass ampoule (Solvent) | 1 vial and 1 ampoule per pack (all strengths) | Intravenous<br>Subcutaneous           |
| <b><u>Member State</u></b> | <b><u>Marketing Authorisation Holder</u></b>  | <b><u>Tradename Name</u></b> | <b><u>Strength</u></b>        | <b><u>Pharmaceutical Form</u></b>             | <b><u>Packaging</u></b>                        | <b><u>Package Size</u></b>                    | <b><u>Route of Administration</u></b> |
| Sweden                     | Schering-Plough Europe<br>Rue de Stalle 73,<br>B-1180 Brussels<br>BELGIUM<br><u>Agent:</u><br>Novartis Sverige AB, PO Box 1150,<br>S-183 11 Täby SWEDEN | Leucomax                     | 150 mcg<br>300 mcg<br>400 mcg | Powder and solvent for solution for injection | Glass vial (Powder)<br>Glass ampoule (Solvent) | 1 vial and 1 ampoule per pack (all strengths) | Intravenous<br>Subcutaneous           |
| United Kingdom             | Schering-Plough Ltd<br>Shire Park, Welwyn Garden City,<br>Hertfordshire, AL7 1TW,<br>UK   | Leucomax                     | 150 mcg<br>300 mcg<br>400 mcg | Powder and solvent for solution for injection | Glass vial (Powder)<br>Glass ampoule (Solvent) | 1 vial and 1 ampoule per pack (all strengths) | Intravenous<br>Subcutaneous           |



**ANNEX III**

**AMENDED SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

LEUCOMAX / MIELOGEN / SCH39300

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

| Active ingredient                     | Quantity per vial                                     |                                   |               |
|---------------------------------------|---|-----------------------------------|---------------|
| Molgramostim:<br>I.U.<br>(micrograms) | 1.67x10 <sup>6</sup><br>4.44x10 <sup>6</sup><br>(150) | 3.33x10 <sup>6</sup><br><br>(300) | <br><br>(400) |

Molgramostim, a recombinant human granulocyte-macrophage colony stimulating factor (rHuGM-CSF), is a water-soluble, non-glycosylated protein with isoleucine at position 100. It contains 127 amino acids and has a molecular weight of 14,477 daltons. Molgramostim is produced by a strain of *Escherichia coli* bearing a genetically engineered plasmid which contains a human GM-CSF gene.

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Sterile, lyophilized powder to be reconstituted with sterilized water for injections for intravenous or subcutaneous administration.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

LEUCOMAX / MIELOGEN / SCH39300 is indicated to reduce the risk of infection due to neutropenia in patients treated with cytotoxic chemotherapy for malignant diseases (see section 4.4, Special precautions for use, Laboratory tests). This risk of infection due to neutropenia, and therefore the clinical benefit of LEUCOMAX / MIELOGEN / SCH39300 treatment, depends on the intensity of the cytotoxic chemotherapy administered.

LEUCOMAX / MIELOGEN / SCH39300 is indicated for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by autologous bone marrow transplantation (BMT), in patients considered to be at increased risk of prolonged severe neutropenia and in patients with evidence of graft failure.

There is insufficient clinical trial data on the use of LEUCOMAX / MIELOGEN / SCH39300 after allogeneic BMT or after peripheral blood stem cells (PBSC) transplantation to recommend its use.

### 4.2 Posology and method of administration

LEUCOMAX / MIELOGEN / SCH39300 dosing regimens vary according to the indication for therapy. The maximum daily dose of LEUCOMAX / MIELOGEN / SCH39300 should not exceed 0.11 million I.U./kg (10 micrograms/kg).

LEUCOMAX / MIELOGEN / SCH39300 must be reconstituted before administration. (See section 6.6 for reconstitution instructions.)

The recommended dosage regimens are:

### **Cancer chemotherapy**

0.06 to 0.11 million I.U./kg per day (5 to 10 micrograms/kg per day) administered subcutaneously. Treatment should **not** be initiated concurrently with chemotherapy but should begin at least 24 hours after the last dose of chemotherapy and continued for 7 to 10 days. Dosing may be initiated at 0.06 million I.U./kg per day (5 micrograms/kg per day).

### **Bone marrow transplantation (BMT)**

0.11 million I.U./kg per day (10 micrograms/kg per day) intravenously; administer infusion over 4 to 6 hours for a maximum of 30 days, beginning the day after BMT.

Continue until absolute neutrophil count (ANC) is  $\geq 1000/\text{mm}^3$ .

## **4.3 Contraindications**

LEUCOMAX / MIELOGEN / SCH39300 is contraindicated:

- in patients with a history of hypersensitivity to molgramostim or any component of the injectable formulation.
- for concomitant use with wide field radiotherapy as patients treated with GM-CSF had increased incidence of pulmonary adverse events, including fatalities.
- for the purpose of increasing the dose intensity of cytotoxic chemotherapy beyond established dosage regimens.

## **4.4 Special warnings and special precautions for use**

### **Special warnings**

LEUCOMAX / MIELOGEN / SCH39300 should be used under the supervision of a physician experienced in the treatment of oncological and haematopoietic disorders or infectious diseases.

The first dose of LEUCOMAX / MIELOGEN / SCH39300 should be administered under medical supervision.

### **Special precautions for use**

Acute, severe, life-threatening hypersensitivity reactions, including anaphylaxis, angioedema or bronchoconstriction, have occurred in patients receiving LEUCOMAX / MIELOGEN / SCH39300. If such reactions occur, LEUCOMAX / MIELOGEN / SCH39300 should be withdrawn immediately and not re-introduced.

LEUCOMAX / MIELOGEN / SCH39300 should be used with caution in neutropenic patients receiving chemotherapy for myeloid malignancies. The benefit of a reduced neutropenic period in such patients must be balanced against the theoretical risk of tumour growth associated with cytokine stimulation. LEUCOMAX / MIELOGEN / SCH39300 should not be used in patients with more than 5% myeloblasts in the bone marrow and/or peripheral blood after completion of chemotherapy.

In clinical studies, LEUCOMAX / MIELOGEN / SCH39300 has been associated infrequently\* with pericarditis and rarely\* with pleuritis, pleural and pericardial effusion. If such reactions occur, LEUCOMAX / MIELOGEN / SCH39300 should be withdrawn.

Patients with pre-existing pulmonary disease may be predisposed to decreased pulmonary function and dyspnoea, and should be monitored closely when being treated with LEUCOMAX / MIELOGEN / SCH39300.

The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs leading to respiratory failure or adult respiratory distress syndrome (ARDS). Consider discontinuation of LEUCOMAX / MIELOGEN / SCH39300 and give appropriate treatment.

In clinical trials, adverse events reported with initiation of dosing were mostly mild to moderate in severity, and included rigors, dyspnea, fever, nausea, vomiting, non-specific chest pain, asthenia, hypotension or flushing. These symptoms, which infrequently required withdrawal of LEUCOMAX / MIELOGEN / SCH39300, were managed symptomatically.

In a few isolated instances, autoimmune disease developed or was exacerbated during rHuGM-CSF therapy; therefore, when administering LEUCOMAX / MIELOGEN / SCH39300 to patients with a history of, or predisposition to autoimmune disease including autoimmune thrombocytopenia, this should be considered.

Patients receiving LEUCOMAX / MIELOGEN / SCH39300 are at greater risk of thrombocytopenia. Regular monitoring of the platelet count and haematocrit is recommended.

**Laboratory tests** – Standard haematological tests (complete blood count, and differential and platelet count) should be performed and serum albumin levels monitored during therapy with LEUCOMAX / MIELOGEN / SCH39300.

**Paediatric use** – The safety of LEUCOMAX / MIELOGEN / SCH39300 has been demonstrated in a limited number of patients under the age of 18 years. There are no apparent differences in the reported treatment-related adverse events between these patients and adult patients.

**Use in the elderly** – There are no apparent differences in safety of LEUCOMAX / MIELOGEN / SCH39300 between elderly and non-elderly patients.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Since dosing with LEUCOMAX / MIELOGEN / SCH39300 has been associated with a decrease in serum albumin, drugs that are highly bound to serum albumin may require dosage adjustment.

Although with LEUCOMAX / MIELOGEN / SCH39300 no adverse drug interaction has been reported, the possibility of a drug-drug interaction cannot be excluded completely.

#### **4.6 Pregnancy and lactation**

Safety of LEUCOMAX / MIELOGEN / SCH39300 for use in human pregnancy has not been established. Animal studies have shown reproductive toxicity. In primate models, administration of molgramostim was associated with fetal death and spontaneous abortion at doses of 0.07 and 0.11 million I.U./kg per day (6 and 10 micrograms/kg per day).

In the absence of clinical data in pregnancy, the therapeutic benefit to the patient must be weighed against potential risks to the progress of the pregnancy.



**Nursing mothers** – It is not known whether LEUCOMAX / MIELOGEN / SCH39300 is excreted in human milk. However, because of the potential for adverse effects in infants, nursing is not recommended in women receiving LEUCOMAX / MIELOGEN / SCH39300.

**Effect on fertility** – Studies in humans to determine effects of LEUCOMAX / MIELOGEN / SCH39300 on fertility have not been undertaken.

#### **4.7 Effects on ability to drive and use machines**

None known.

#### **4.8 Undesirable effects**

Since many of the undesirable effects reported during LEUCOMAX / MIELOGEN / SCH39300 clinical trials are often associated with underlying or concurrent diseases or their treatment, the causal relationship of these effects to LEUCOMAX / MIELOGEN / SCH39300 cannot be definitively determined. Most adverse reactions observed were mild or moderate in severity. Rarely were they severe or life threatening.

Frequently\* reported undesirable effects across all indications were fever, nausea, dyspnoea, diarrhoea, rash, rigors, injection-site reaction (with subcutaneous administration), vomiting, fatigue, anorexia, musculoskeletal pain and asthenia.

Infrequently\* reported events included: non-specific chest pain, stomatitis, headache, increased sweating, abdominal pain, pruritus, dizziness, peripheral oedema, paresthesia and myalgia, anaphylaxis, bronchospasm, cardiac failure, confusion, hypotension, cardiac rhythm abnormalities, pericarditis, pulmonary oedema.

Serious reactions, which occurred rarely\* in clinical trials, included: capillary leak syndrome, cerebrovascular disorders, convulsions, hypertension, intracranial hypertension, pericardial effusion, pleural effusion, and syncope.

Cases of pulmonary infiltrates have been reported; in a few cases the outcome was respiratory failure or adult respiratory distress syndrome (ARDS), which may be fatal.

**Laboratory findings** – In all patient groups the most frequently occurring changes in laboratory values were decreased platelet count, decreased haemoglobin level, decreased serum albumin level and increased eosinophils (absolute count and percent). Because of the association with myelosuppressive chemotherapy, the causal relationship of these changes to LEUCOMAX / MIELOGEN / SCH39300 is difficult to evaluate.

The frequency of antibodies that bind to molgramostim, measured by enzyme-linked immunosorbent assay (ELISA) and bioassay, was determined to be 1% post treatment. No loss of activity of LEUCOMAX / MIELOGEN / SCH39300 was evident in these patients.

#### **4.9 Overdose**

As for any pharmacologically active compound, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated when severe reactions, as described above, occur. In some patients receiving doses of 20 to 30 micrograms/kg per day, the following symptoms have been observed: tachycardia, hypotension, dyspnoea, and flu-like symptoms. These symptoms abated quickly on symptomatic treatment.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Cytokines, ATC code: L03 A A03

Granulocyte-macrophage colony stimulating factor is a multi-lineage glycoprotein regulator involved in both the regulation of haematopoiesis and the activation of mature myeloid cells. *In vitro*, the recombinant human GM-CSF, molgramostim, stimulates the proliferation and differentiation of haematopoietic precursor cells that result in the production of granulocytes, monocytes/macrophages and T lymphocytes.

Studies on fresh tumour explants in the human tumour clonogenic assay have demonstrated that molgramostim neither stimulates nor inhibits tumour cell growth. rHuGM-CSF can enhance expression of major histocompatibility class II antigens on human monocytes and can augment antibody production. In addition, rHuGM-CSF exhibits marked effects on the functional activity of mature neutrophils, including enhanced phagocytosis of bacteria, enhanced cytotoxicity toward malignant cells and priming of neutrophils for enhanced oxidative metabolism, an important reaction related to host defence.

Intravenous bolus or subcutaneous administration of molgramostim to cynomolgus monkeys results in significant increases in the circulating white blood cell (WBC) count. Serial differential counts indicate that this increase is due mainly to neutrophilic granulocytes and, secondarily, to lymphocytes and eosinophils. In a study of the kinetics of response, the effect of a single dose of molgramostim was usually apparent within 1 to 4 hours and peaked within 6 to 18 hours after initiation of dosing. Results of a dose-response study in cynomolgus monkeys utilizing intravenous bolus injections of molgramostim for 5 consecutive days indicate that maximal response can be achieved at 0.17 million I.U./kg per day (15 micrograms/kg per day). Molgramostim has also been shown to stimulate WBC count in a leucopenic cynomolgus monkey treated previously with cyclophosphamide.

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

#### **Effects observed in clinical trials in chemotherapy setting**

In a randomized, double-blind trial with 172 high-grade non-Hodgkin's Lymphoma patients treated with COP-BLAM, administration of GM-CSF reduced the risk of infection. Also, a small increase in dose intensity of COP-BLAM was observed which was not translated into increased survival.

#### **Effects observed in clinical trials in autologous bone marrow transplantation setting**

In a randomized trial in 408 patients treated with GM-CSF or placebo after myeloablative therapy (predominantly for non-Hodgkin's Lymphoma and Hodgkin's disease) followed by autologous bone marrow or peripheral stem cell transplantation, patients in the GM-CSF arm showed a shortened duration of neutropenia. However, relevant differences in outcome for GM-CSF and placebo, in particular in terms of risk of infection, have not been demonstrated.

## **5.2 Pharmacokinetic properties**

Studies in rats showed that radioactivity was extensively distributed following intravenous administration of <sup>125</sup>I-rHuGM-CSF. The drug appeared to be rapidly metabolized and excreted. The pharmacokinetic profiles of molgramostim were similar in monkeys, healthy male volunteers and patients. After subcutaneous doses of 0.03, 0.11 or 0.22 million I.U./kg (3, 10 or 20 micrograms/kg) and following intravenous doses of 0.03 to 0.33 million I.U./kg (3 to 30 micrograms/kg), increases in the total area under curve (AUC) were dose related. Maximum molgramostim serum concentrations were reached within 3 to 4 hours after

subcutaneous administration. Molgramostim had an elimination half-life of 1 to 2 hours following intravenous administration, and 2 to 3 hours following subcutaneous administration. The slightly longer half-life observed after subcutaneous administration is probably due to prolonged absorption from the injection site.

### **5.3 Preclinical safety data**

Although molgramostim is generally recognized to be species specific, acute toxicologic studies were conducted in mice, rats and rabbits. No toxic effects were observed in these species. Single intravenous bolus doses of 2000 micrograms/kg of molgramostim to 2 infant monkeys produced a rise in reticulocytes in the male, and a rise in eosinophils in the female. In monkeys, repeated intravenous bolus injection for up to 1 month at doses ranging to 3.33 million I.U./kg per day (300 micrograms/kg per day – up to 30 times the maximum recommended human daily dose) were generally well tolerated, with haematological changes (increase in white cell count) in the peripheral blood reflecting the pharmacological effect on the bone marrow and extramedullary haematopoietic tissues. Three monkeys in the high-dose group either died or were sacrificed near the end of the dosing period. In these and the monkeys necropsied at the end of 1 month of dosing, enlarged lymph nodes, focal acute inflammatory skin lesions and serositis or polyserositis were present. The effects were progressive and dose related.

In monkeys, subacute administration of suprathreshold doses is responsible for exaggeration of known pharmacological effects.

Molgramostim administered subcutaneously to rats had a potential for causing mild to moderate local irritation. With a single injection into the medial artery of the rabbit ear, minimal local irritation was observed in both molgramostim and vehicle-treated animals. Evaluation of local irritation studies in rhesus monkeys showed that moderate to severe inflammatory lesions occurred in and below the skin at the sites of injection.

Inflammatory lesions were the most significant finding in primates given 1 or 3.33 million I.U./kg (90 or 300 micrograms/kg) of molgramostim (18 to 60 times the human daily dose).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Mannitol; citric acid, anhydrous; dibasic sodium phosphate; polyethylene glycol 3350; human albumin.

### **6.2 Incompatibilities**

The use of silicon catheter materials is not recommended.

### **6.3 Shelf life**

24 months when stored as specified.

### **6.4 Special precautions for storage**

LEUCOMAX / MIELOGEN / SCH39300 sterile lyophilized powder should be stored at 2 to 8°C

and protected from light. Following reconstitution with sterilized water for injections, LEUCOMAX / MIELOGEN / SCH39300 solution can be stored for up to 24 hours when refrigerated at 2 to 8°C. Unused LEUCOMAX / MIELOGEN / SCH39300 solution should be discarded.

## 6.5 Nature and contents of container

LEUCOMAX / MIELOGEN / SCH39300 sterile lyophilized powder is packaged in a Type-I glass vial with butyl or halobutyl rubber closure and aluminium seal.

## 6.6 Instructions for use and handling

**Reconstitution of LEUCOMAX / MIELOGEN / SCH39300** – Add 1.0 ml of sterilized water for injections to the vial of LEUCOMAX / MIELOGEN / SCH39300. Agitate the vial gently to dissolve the powder completely. This provides the labelled amount of LEUCOMAX / MIELOGEN / SCH39300 as an isotonic solution, which may be used for **subcutaneous administration**. When diluted further in accordance with the instructions below, LEUCOMAX / MIELOGEN / SCH39300 may be administered intravenously over 4 to 6 hours while at room temperature.

Discard any unused portion of the reconstituted solution.

**Dilution for intravenous administration** – Dilution directions must be followed carefully to avoid loss of molgramostim as a result of adsorption to the infusion system.

Reconstitute each of the required number of vials of lyophilized powder of the appropriate strength of molgramostim with 1 ml of sterilized water for injections. The reconstituted molgramostim solution must be further diluted in 25 ml, 50 ml or 100 ml infusion bags or bottles of either normal saline solution or 5% dextrose in water. The number and the strength of lyophilized powder vials required must be such that the above infusion admixture solution contains a final concentration of molgramostim of **not less than 0.08 million I.U. (7 micrograms) per ml**. The resulting infusion solution can be stored for up to 24 hours when kept in the refrigerator (2 to 8°C).

Compatibility data are available to support the use of several intravenous sets, including the Travenol I.V. Administration Set 2C0001, Intrafix Air and Infusionsgerät R 87 Plus from Germany, Souplex from France, Travenol C 033 and Steriflex from the UK, Intrafix Air Euroklappe-ISO and Soluset from Spain, and Linfosol set from Italy, for the administration of these solutions. Significant adsorption of LEUCOMAX / MIELOGEN / SCH39300 has been observed in silicon catheter materials; thus, use of such materials is not recommended.

Parenteral drug products should be inspected visually for discoloration and particulate matter prior to administration. The reconstituted solution is colourless to light yellow. For intravenous administration, the use of an in-line, low-protein-binding 0.2 or 0.22 micrometre filter (such as Millipore Durapore) is recommended.

## 7. MARKETING AUTHORISATION HOLDER

## 8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**

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