

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrGRASTOFIL®

filgrastim Injection

Sterile Solution for Injection
Subcutaneous or Intravenous Use Only

300 µg/0.5 mL, 480 µg/0.8 mL in single-use pre-filled syringe

Hematopoietic Agent
Granulocyte Colony Stimulating Factor

Apotex Inc.
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Submission Control No: 211537

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RECENT MAJOR LABEL CHANGES

DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING, (Section 6)
OCT, 2016

WARNINGS AND PRECAUTIONS, Glomerulonephritis, (Section 8), OCT, 2016

ADVERSE REACTIONS, Post-Market Adverse Reactions, (Section 9.6), OCT, 2016

PATIENT MEDICATION INFORMATION, OCT, 2016

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Grastofil® (filgrastim Injection) is a biosimilar biologic drug (biosimilar) to Neupogen.

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

Indications have been granted on the basis of similarity between Grastofil® and the reference biologic drug Neupogen.

Grastofil® (filgrastim) is indicated for:

- **Cancer Patients Receiving Myelosuppressive Chemotherapy**

Grastofil® (filgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies (see **Patients with Acute Myeloid Leukemia**) receiving myelosuppressive anti-neoplastic drugs.

Grastofil® is indicated in adult and pediatric patients with cancer receiving myelosuppressive chemotherapy.

A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and twice per week (see **Monitoring and Laboratory Tests**) during Grastofil® therapy to avoid leukocytosis and to monitor the neutrophil count. In phase 3 clinical studies, Grastofil® therapy was discontinued when the ANC was $> 10 \times 10^9/L$ after expected chemotherapy-induced nadir.

- **Patients with Acute Myeloid Leukemia**

Grastofil® is indicated for the reduction in the duration of neutropenia, fever, antibiotic use and hospitalization, following induction and consolidation treatment for acute myeloid leukemia.

- **Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation**

Grastofil® is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients undergoing myeloablative therapy followed by bone marrow transplantation. A CBC and platelet count should be obtained at a minimum of 3 times per week following marrow infusion to monitor marrow reconstitution (see **Monitoring and Laboratory Tests**).

- **Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy**

Grastofil® is indicated for the mobilization of autologous peripheral blood progenitor cells in order to accelerate haematopoietic recovery by infusion of such cells, supported by Grastofil®, after myelosuppressive or myeloablative chemotherapy (see **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG**).

- **Patients with Severe Chronic Neutropenia (SCN)**

Grastofil® is indicated for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infection in patients with a diagnosis of congenital, cyclic or idiopathic neutropenia (see **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG**).

- **Patients with HIV Infection**

Grastofil[®] is indicated in patients with HIV infection for the prevention and treatment of neutropenia, to maintain a normal ANC (eg, between 2×10^9 and $10 \times 10^9/L$). Grastofil[®] therapy reduces the clinical sequelae associated with neutropenia (eg, bacterial infections) and increases the ability to deliver myelosuppressive medications used for the treatment of HIV and its associated complications (see **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG**). It is recommended that complete blood counts and platelet counts be monitored at regular intervals (e.g., initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter, or as clinically indicated) during Grastofil[®] therapy (see **Monitoring and Laboratory Tests**).

2. CONTRAINDICATIONS

Grastofil[®] (filgrastim) is contraindicated in patients with known hypersensitivity to *E. coli* derived products, filgrastim, pegfilgrastim, or to any component of the product. For a complete listing of the components, see the **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the product monograph

3. SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Splenic ruptures, including fatal cases, have been reported following the administration of filgrastim (see **WARNINGS AND PRECAUTIONS, General**).
- Severe sickle cell crises, in some cases resulting in death, have been associated with the use of filgrastim in patients with sickle cell trait or sickle cell disease (see **WARNINGS AND PRECAUTIONS: Hematologic**).

4. DOSAGE AND ADMINISTRATION

Grastofil[®] (filgrastim) is supplied in pre-filled graduated syringes with UltraSafe Passive[®] Needle Guards to prevent accidental needle stick injury. When the pre-filled syringe is emptied of all the medication, the passive needle-guard mechanism pushes over the needle, withdrawing it from the skin and covering it completely. The pre-filled syringe should be disposed of by placing the entire pre-filled syringe with guard activated into an approved puncture-proof container.

The pre-filled syringe system contains natural rubber (a derivative of latex), which should not be handled by persons sensitive to this substance.

*BD UltraSafe Passive[®] is a trademark of Safety Syringes, Inc., parent company is Becton, Dickinson and Company.

4.1 Dosing Considerations

- **Cancer Patients Receiving Myelosuppressive Chemotherapy**

Grastofil[®] should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Grastofil[®] should not be administered in the period 24 hours before the administration of chemotherapy (see **WARNINGS AND PRECAUTIONS**).

- **Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation**

Grastofil® should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

- **Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy**

The first dose should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after PBPC infusion.

4.2 Recommended Dose and Dosage Adjustment

Cancer Patients Receiving Myelosuppressive Chemotherapy

The recommended starting dose of Grastofil® in adult patients is 5 µg/kg/day, administered as a single daily injection by subcutaneous bolus injection, by short intravenous infusion (15 to 30 minutes), or by continuous subcutaneous or continuous intravenous infusion.

The recommended dose in pediatric oncology patients is 5 µg/kg/day administered subcutaneously.

A CBC and platelet count should be obtained before instituting Grastofil® therapy, and monitored twice weekly during therapy. Doses may be increased in increments of 5 µg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir. Therapy should be discontinued if the ANC surpasses $10 \times 10^9/L$ after the ANC nadir has occurred.

Grastofil® should be administered daily for up to 2 weeks, until the ANC has reached $10 \times 10^9/L$ following the expected chemotherapy-induced neutrophil nadir. The duration of Grastofil® needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Grastofil® therapy should be discontinued if the ANC surpasses $10 \times 10^9/L$ after the expected chemotherapy-induced neutrophil nadir (see **WARNINGS AND PRECAUTIONS**). In phase 3 trials, efficacy was observed at doses of 4 to 8 µg/kg/day.

Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

The recommended dose of Grastofil® following bone marrow transplant is 10 µg/kg/day given as an intravenous infusion of 4 to 24 hours, or a continuous 24-hour subcutaneous infusion. During the period of neutrophil recovery, the daily dose of Grastofil® should be titrated against the neutrophil response as follows:

Absolute Neutrophil Count	Grastofil® Dose Adjustment
When ANC > $1.0 \times 10^9/L$ for 3 consecutive days	Reduce to 5 µg/kg/day* (see below)
then: If ANC remains > $1.0 \times 10^9/L$ for 3 more consecutive days	Discontinue Grastofil®
If ANC decreases to < $1.0 \times 10^9/L$	Resume at 5 µg/kg/day

*If ANC decreases to < $1.0 \times 10^9/L$ at any time during the 5 µg/kg/day administration, Grastofil® should be increased to 10 µg/kg/day, and the above step should then be followed.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

The recommended dose of Grastofil® for PBPC mobilization is 10 µg/kg/day given as a single daily subcutaneous injection or a continuous 24-hour infusion. Grastofil® therapy should be given for at least 4 days before the first leukapheresis procedure, and should be continued through to the day of the last leukapheresis procedure. Collections should be commenced on day 5 and continued on consecutive days until the desired yield of haematopoietic progenitor cells is obtained. For peripheral blood progenitor cells mobilized with Grastofil®, a schedule of leukapheresis collections on days 5, 6, and 7 of a 7-day treatment regimen has been found to be effective.

The target number of progenitor cells to be collected and re-infused is to be determined by the treating physician. The following should be considered:

- A minimum or optimal number of progenitor cells in the leukapheresis product, needed for adequate hemopoietic reconstitution, have not been determined. However, studies indicate that the infusion of higher numbers of progenitor cells appears to be associated with a shorter time to neutrophil and platelet recovery.
- Tests for quantifying the progenitor cells, measured as CD34+ or GM-CFU, are not standardized and variations may exist between laboratories, and
- Factors other than Grastofil® dosage, such as prior cytotoxic chemo- or radio-therapy, may affect the number and quality of progenitor cells mobilized and collected by leukapheresis.

The recommended dose of Grastofil® following PBPC transplant is 5 µg/kg/day given either subcutaneously or as an intravenous infusion. The daily dose of Grastofil® should be titrated according to the schedule provided above (**Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation**).

Patients with HIV Infection

The recommended starting dose of Grastofil® is 1 µg/kg/day or 300 µg 3 times per week by subcutaneous injection until a normal neutrophil count is reached and can be maintained (ANC $\geq 2 \times 10^9/L$). Dose adjustments may be necessary as determined by the patient's ANC to maintain the ANC between $2 \times 10^9/L$ and $10 \times 10^9/L$.

When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. An initial dose of 300 µg 3 times per week by subcutaneous injection is recommended. A further dose adjustment may be necessary to maintain the ANC between $2 \times 10^9/L$ and $10 \times 10^9/L$.

In clinical trials, the maximum filgrastim dose did not exceed 10 µg/kg/day.

Patients with Severe Chronic Neutropenia

• Starting Dose

Congenital Neutropenia: The recommended daily starting dose is 12 µg/kg subcutaneously (single or divided dose).

Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 µg/kg subcutaneously (single or divided dose).

- **Dose Adjustments**

Grastofil® may be administered subcutaneously as a single daily injection to increase and sustain the ANC above $1.5 \times 10^9/L$. Chronic daily administration is required to maintain an adequate neutrophil count. After 1 to 2 weeks of therapy the initial dose maybe doubled or halved. Subsequently, the dose maybe individually adjusted not more than every 1 to 2 weeks to maintain the ANC between $1.5 \times 10^9/L$ and $10 \times 10^9/L$. WBC/ANC monitoring should be done more frequently (e.g. every other day) if the ANC reaches values above $25 \times 10^9/L$ and the dose reduced if the ANC remains greater than $25 \times 10^9/L$ for 1 week. In the SCN post-marketing surveillance study, the median daily doses of filgrastim reported (median duration 4.4 years) were: Congenital Neutropenia 6.9 µg/kg; Cyclic Neutropenia 2.1 µg/kg; Idiopathic Neutropenia 1.2 µg/kg.

In clinical trial in patients with SCN, 91% of patients who responded to filgrastim therapy responded at doses of ≤ 12 µg/kg. Ninety-seven percent of patients responded at doses of ≤ 24 µg/kg/day. Therefore, patients with SCN who do not respond to the recommended starting dose should be treated with up to 24 µg/kg/day in order to determine if they will respond. In some cases, where higher doses were tried, an improvement in the ANC and the clinical condition was seen with a few patients only.

4.3 Administration

Grastofil® is intended for subcutaneous injection or intravenous use and should not be given by any other route of administration.

Grastofil® should not be vigorously shaken.

In those situations in which the physician determines that the patient can safely and effectively self-administer Grastofil®, the patient should be instructed as to the proper dosage and administration. If home use is prescribed, patients should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes or drug product. A puncture-proof container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician.

Dilution

If required, Grastofil® may be diluted in 5% dextrose. Grastofil® diluted to a concentration between 5 and 15 µg/mL should be protected from adsorption to plastic materials by the addition of albumin (human) at a concentration of 2.0 mg/mL (see **STORAGE, STABILITY AND DISPOSAL**).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

When diluted in 5% dextrose, Grastofil® is compatible with glass bottles. When diluted in 5% dextrose plus albumin, Grastofil® is compatible with PVC or polyolefin intravenous bags.

Dilution of Grastofil® to a final concentration of < 5 µg/mL even in the presence of albumin (human) is not recommended at any time. **Do not dilute with saline at any time; product may precipitate.**

4.4 Reconstitution

Not Applicable

4.5 Missed Dose

Grastofil® should be injected at the same time each day. Patients who miss a dose of Grastofil® are advised to contact their doctor or nurse.

5. OVERDOSAGE

The maximum tolerated dose of filgrastim has not been determined. In dose ranging studies, 5 of 16 patients given $\geq 69 \mu\text{g}/\text{kg}/\text{day}$ were withdrawn due to adverse experiences. In these and other clinical trials, only 2 of 253 patients on lower doses were withdrawn due to adverse events.

In filgrastim clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC counts $> 100 \times 10^9/\text{L}$ have been reported in less than 2% of patients and were not associated with any reported adverse clinical effects.

It is recommended, to avoid the potential risks of excessive leukocytosis, that filgrastim therapy should be discontinued if the ANC surpasses $10 \times 10^9/\text{L}$ after the chemotherapy-induced ANC nadir has occurred.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

For management of a suspected drug overdose, contact your regional poison control centre.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous (SC) or Intravenous (IV)	Sterile Solution for Injection / 300 $\mu\text{g}/0.5 \text{ mL}$ and 480 $\mu\text{g}/0.8 \text{ mL}$	acetate polysorbate 80 sodium sorbitol water

Grastofil® (filgrastim) is a sterile, clear, colourless, preservative-free liquid for parenteral administration. Each single-use pre-filled syringe contains either:

- 300 $\mu\text{g}/0.5 \text{ mL}$ (600 $\mu\text{g}/\text{mL}$) of filgrastim formulated in a sodium acetate buffer at pH 4.0 (acetate 0.295 mg; sodium 0.0175 mg), containing sorbitol (25.00 mg), polysorbate 80 (0.004% w/v) and water for injection (q.s. to 0.5mL), or
- 480 $\mu\text{g}/0.8 \text{ mL}$ (600 $\mu\text{g}/\text{mL}$) of filgrastim formulated in a sodium acetate buffer at pH 4.0 (acetate 0.472 mg; sodium 0.028 mg), containing sorbitol (40.00 mg), polysorbate 80 (0.004% w/v) and water for injection (q.s. to 0.8 mL).

Availability of Dosage Forms

Pre-filled Syringes

Grastofil[®] will be available in 1 mL, glass (USP Type I), single use pre-filled graduated syringes with an UltraSafe Passive[®] Needle-Guard in two sizes, 300 µg/0.5 mL and 480 µg/0.8 mL (both containing 600 µg/mL of filgrastim). The pre-filled syringes have 1/40 printed markings for graduations from 0.1 mL to 1.0 mL on the syringe barrel.

Grastofil[®] will be supplied in cartons of one and ten individually blistered pre-filled syringes in a carton (1×1 and 1×10, respectively) along with the package insert.

The pre-filled syringe system contains natural rubber (a derivative of latex), which should not be handled by persons sensitive to this substance.

7. DESCRIPTION

Grastofil[®] (filgrastim) is a biosimilar biologic drug that is a recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF) produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein produced by *Escherichia coli* (*E.coli*) bacteria into which has been inserted the human granulocyte colony stimulating factor gene. Filgrastim has a molecular weight of 18,800 Daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression of *E.coli*.

8. WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

- **Splenic Rupture**

Splenic ruptures, including fatal cases, have been reported following the administration of filgrastim. Patients receiving Grastofil[®] (filgrastim) who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

- **Simultaneous Use with Chemotherapy**

The safety and efficacy of Grastofil[®] given simultaneously with cytotoxic chemotherapy have not been established. Studies in adult patients showed that an interaction between concurrent filgrastim and 5-fluorouracil (5-FU) is possible and can result in a paradoxical fall in ANC. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use Grastofil[®] in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy (see **DOSAGE AND ADMINISTRATION**).

The efficacy of Grastofil[®] has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (e.g. nitrosoureas) or with mitomycin C or with myelosuppressive doses of anti-metabolites such as 5-FU or cytosine arabinoside.

The safety and efficacy of Grastofil[®] have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of Grastofil[®] with chemotherapy and radiation therapy should be avoided.

Carcinogenesis and Mutagenesis

The carcinogenic potential of Grastofil[®] has not been studied. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. Filgrastim had no observed effect on the fertility of male or female rats, or on gestation at doses up to 500 µg/kg.

- **Growth Factor Potential**

Grastofil[®] is a growth factor that primarily stimulates production of neutrophils. However, the possibility that Grastofil[®] can act as a growth factor for certain tumor types cannot be excluded. Randomized studies have demonstrated that treatment with filgrastim following chemotherapy for acute myeloid leukemia does not adversely influence the outcome of treatment. The use of filgrastim in chronic myeloid leukemia (CML) and myelodysplasia (MDS) has not been fully investigated, and caution should be exercised in using this drug in patients with CML or MDS.

Tumor cells may be collected in the leukapheresis product, following PBPC mobilization by filgrastim. The clinical significance and the effect of reinfusion of tumor cells with the leukapheresis product are still unknown and the possible contribution of clonogenic tumor cells to an eventual relapse has not been determined.

Acute myeloid leukaemia (AML) has been reported to occur in the natural history of severe chronic neutropenia without cytokine therapy. It is not known what, if any, additional risk may be imposed by Grastofil[®] therapy.

Cardiovascular

Cardiac events (myocardial infarctions, arrhythmias) have been reported in 11 of 375 cancer patients receiving filgrastim in clinical studies; the relationship to filgrastim therapy is unknown. However, patients with pre-existing cardiac conditions receiving Grastofil[®] should be monitored closely.

Capillary Leak Syndrome

Capillary Leak Syndrome (CLS) has been reported after the administration of filgrastim or pegfilgrastim. CLS may cause circulatory shock and may be fatal, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity, and maybe life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive treatment, which may include a need for intensive care.

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Hematologic

Severe sickle cell crises, in some cases resulting in death, have been associated with the use of filgrastim in patients with sickle cell trait or sickle cell disease. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell trait and sickle cell disease should prescribe Grastofil[®] for such patients, and only after careful consideration of the potential risks and benefits.

The response to Grastofil® may be diminished in patients with reduced neutrophil precursors such as those previously treated with extensive dose chemotherapy or radiotherapy.

In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see **ADVERSE REACTIONS**). As a result of the potential of receiving higher doses of chemotherapy (ie, full doses on the prescribed schedule), the patient may be at greater risk of thrombocytopenia, anemia, and non-haematological consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used). Regular monitoring of the hematocrit and platelet count is recommended.

- **Leukocytosis**

- **Cancer Patients Receiving Myelosuppressive Chemotherapy**

- In all studies, including phase 1/2 dose ranging studies, WBC counts of $100 \times 10^9/L$ or greater were observed in approximately 2% of patients receiving filgrastim at doses above 5 and up to 115 $\mu g/kg/day$. There were no reports of adverse events associated with this degree of leukocytosis. In order to avoid the potential complications of excessive leukocytosis, a complete blood count (CBC) is recommended twice per week during filgrastim therapy (see **Monitoring and Laboratory Tests**).

- **Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy**

- During the period of administration of Grastofil® for PBPC mobilization in cancer patients, discontinuation of Grastofil® is appropriate if the leukocyte count rises to $> 100 \times 10^9/L$ (see **Monitoring and Laboratory Tests**).

- **Thrombocytopenia**

Thrombocytopenia has been reported in patients receiving filgrastim. Platelet counts should be monitored closely.

Hypersensitivity/Allergic Reactions

Hypersensitivity, including serious allergic-type reactions and anaphylactic reactions occurring on initial or subsequent treatment have been reported in < 1 in 4,000 patients treated with filgrastim. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticarial, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving filgrastim intravenously. Rapid resolution of symptoms occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged. Do not administer Grastofil® to patients with a history of allergic reactions to filgrastim or pegfilgrastim (see **CONTRAINDICATIONS**). If a serious allergic reaction or anaphylactic reaction occurs, appropriate therapy should be administered and Grastofil® should be permanently discontinued.

- **Cutaneous Vasculitis**

Cutaneous vasculitis has been reported in patients treated with filgrastim. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Symptoms of vasculitis generally developed simultaneously with an increase in the ANC and abated when the ANC decreased. Many patients were able to continue filgrastim at a reduced dose.

Immune

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving the reference product (Neupogen) has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim, the nature and specificity of these antibodies has not been adequately studied. In clinical studies comparing filgrastim to pegfilgrastim, the incidence of antibodies binding to filgrastim was 3% (11/333). In these 11 patients, no evidence of a neutralizing response was observed using a cell-based bioassay. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including timing of sampling, sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to filgrastim with the incidence of antibodies to other products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against filgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia; however, this has not been reported in clinical studies or in post-marketing experience. Patients who develop hypersensitivity to filgrastim may have allergic or hypersensitivity reactions to other *E.coli*-derived proteins.

Monitoring and Laboratory Tests

- ***Cancer Patients Receiving Myelosuppressive Chemotherapy***

A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and at regular intervals (twice per week) during Grastofil[®] therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when filgrastim was administered, and white blood cells (WBC) differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced, and was followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of WBC counts, particularly at the time of the recovery from the post chemotherapy nadir, is recommended in order to avoid excessive leukocytosis.

- ***Cancer Patients Receiving Myeloblastic Chemotherapy Followed by Bone Marrow Transplantation***

A CBC and platelet count should be obtained at regular intervals (3 times per week during Grastofil[®] therapy) following marrow infusion.

- ***Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy***

After 4 days of Grastofil[®] treatment for PBPC mobilization, neutrophil counts should be monitored. Monitoring of platelet and red blood cell counts is recommended during the leukapheresis period. Frequent CBCs and platelet counts are recommended (at least 3 times per week) following PBPC reinfusion.

- **Patients with Severe Chronic Neutropenia**

During the initial 4 weeks of Grastofil® therapy, and for 2 weeks following any dose adjustment, a CBC with differential and platelet determination should be performed twice weekly. Once a patient is clinically stable, a CBC with differential and platelet determination should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular CBCs (i.e. as clinically indicated but at least quarterly) is recommended. Patients should be monitored for the possible occurrence of bone density changes while on long-term Grastofil® therapy. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment.

In clinical trials with filgrastim, the following laboratory results were observed:

- Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of filgrastim therapy,
- Platelet counts were generally at the upper limits of normal prior to filgrastim therapy. With filgrastim therapy, platelet counts decreased but generally remained within normal limits (see **ADVERSE REACTIONS**),
- Early myeloid forms were noted in the peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients,
- Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with filgrastim therapy.
- As in other trials, increases were observed in serum uric acid, lactic dehydrogenase, and serum alkaline phosphatase.

- **Patients with HIV Infection**

A CBC and platelet count should be obtained prior to starting Grastofil® therapy and at regular intervals (e.g. initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter, or as clinically indicated) during Grastofil® therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial doses of Grastofil®. It is recommended that blood samples be drawn for ANC measurement prior to any scheduled dosing with Grastofil®.

Respiratory

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients receiving filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, filgrastim should be either withheld until resolution of ARDS or discontinued. Patients should receive appropriate medical management for this condition.

Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization has been reported in healthy donors undergoing peripheral blood progenitor cell (PBPC) mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of Grastofil® for PBPC mobilization in healthy donors is not an approved indication.

Other

- **Cancer Patients Receiving Myelosuppressive Chemotherapy**
 - **Premature Discontinuation of Filgrastim Therapy**

A transient increase in neutrophil counts is typically seen 1-2 days after initiation of

filgrastim therapy. However, for a sustained therapeutic response, Grastofil[®] therapy should be continued following chemotherapy until the post nadir ANC reaches $10 \times 10^9/L$. Therefore, the premature discontinuation of filgrastim therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see **DOSAGE AND ADMINISTRATION**)

- **Risks Associated with Increased Doses of Chemotherapy**

Intensified doses of chemotherapeutic agents may lead to increased toxicities associated with these agents, including cardiac, pulmonary, neurologic, and dermatologic effects (please refer to the product monograph of the specific chemotherapy agents used). Increased exposure to alkylating agents, particularly if combined with radiotherapy, is known to be associated with the genesis of secondary malignancies. When considering chemotherapy dose intensification with Grastofil[®] support, clinicians should weigh the risk of secondary malignancy against the potential benefits of improved primary disease outcome.

- **Patients with Severe Chronic Neutropenia**

- **Diagnosis of Congenital, Cyclic or Idiopathic Neutropenia**

Care should be taken to confirm the diagnosis of congenital, cyclic or idiopathic neutropenia, which may be difficult to distinguish from myelodysplasia before initiating Grastofil[®] therapy. The safety and efficacy of Grastofil[®] in the treatment of neutropenia or pancytopenia due to other haematopoietic disorders (e.g. myelodysplastic syndrome) has not been established.

It is therefore essential that serial complete blood counts with differential and platelet counts and an evaluation of bone marrow morphology and karyotype, be performed prior to initiation of Grastofil[®] therapy.

Myelodysplasia (MDS) and acute myeloid leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS and AML have been observed in patients treated with filgrastim for aplastic anemia and severe chronic neutropenia (SCN). Based on available data, the risk of developing MDS and AML has been confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics has been associated with the eventual development of myeloid leukemia. The effect of continued filgrastim administration in patients with abnormal cytogenetics is unknown. If a patient with SCN develops abnormal cytogenetics, the risks and benefits of continuing filgrastim should be carefully considered (see **ADVERSE REACTIONS**).

- **Chronic Administration**

The safety and efficacy of chronic daily administration of filgrastim in patients with SCN have been established in phase 1/2 clinical trials of 74 patients treated for up to 4.5 years, and in a phase 3 trial of 123 patients treated for up to 3.5 years.

Although the relationship to filgrastim is unclear, osteoporosis has been reported in approximately 7% of patients receiving filgrastim therapy for up to 4.5 years in clinical trials in patients with SCN. Decreased bone density and osteoporosis have also been seen in the pediatric patients with SCN in the post-market setting. Patients with SCN, particularly those patients with congenital neutropenia and those with underlying osteoporotic bone disease, should be monitored for the possible occurrence of bone density changes while on long-term filgrastim therapy. Other infrequently observed

adverse events included exacerbation of some pre-existing skin disorders (e.g. psoriasis), cutaneous vasculitis (leukocytoclastic), alopecia, haematuria/proteinurea, thrombocytopenia (platelets $< 50 \times 10^9/L$).

- **Patients with HIV Infection**

- **Risks Associated with Increased Doses of Myelosuppressive Medications**

- Treatment with filgrastim alone does not preclude thrombocytopenia and anemia due to myelosuppressive medications. As a result of the potential to receive higher doses or a greater number of these medications with filgrastim therapy, the patient may be at a higher risk of developing thrombocytopenia (see **ADVERSE REACTIONS**) and anemia. Regular monitoring of blood counts is recommended.

- **Infections Causing Myelosuppression**

- Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infection or malignancy, consideration should be given to appropriate therapy for treatment of the underlying condition, in addition to administration of Grastofil[®] for treatment of neutropenia.

8.1 Special Populations

8.1.1 Pregnant Women

Filgrastim has been shown to cause adverse effects in pregnant rabbits when given in doses 2 to 10 times the human dose.

In rabbits, increased abortion and embryoletality were observed in animals treated with filgrastim at 80 µg/kg/day. Filgrastim administered to pregnant rabbits at doses of 80 µg/kg/day during the period of organogenesis was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities and decreased body weight, live births and food consumption. External abnormalities were not observed in the fetuses of dams treated at 80 µg/kg/day. Reproductive studies in pregnant rats have shown that filgrastim was not associated with lethal, teratogenic, or behavioural effects on fetuses when administered by daily intravenous injection during the period of organogenesis at dose levels up to 575 µg/kg/day.

In Segment III studies in rats, offspring of dams treated at greater than 20 µg/kg/day exhibited a delay in external differentiation (detachment of auricles and descent of testes) and slight growth retardation possibly due to lower body weight of females during rearing and nursing. Offspring of dams treated at 100 µg/kg/day exhibited decreased body weights at birth and a slightly reduced 4 day survival rate.

There are cases in the literature where the transplacental passage of filgrastim has been demonstrated. Grastofil[®] should be used during pregnancy only if the potential benefit justifies any potential risk to the fetus.

8.1.2 Breast-feeding

It is not known whether filgrastim is excreted in human milk, therefore Grastofil[®] is not recommended for use in nursing women.

8.1.3 Pediatrics

Grastofil® has not been studied in pediatric patients. The data under this subsection are the results of studies in pediatric patients with the reference product.

Cancer Patients Receiving Myelosuppressive Chemotherapy

Data from clinical studies in pediatric patients indicate that the safety of filgrastim is similar in both adults and children receiving cytotoxic chemotherapy.

Twelve pediatric patients with neuroblastoma have received up to 6 cycles of cyclophosphamide, cisplatin, doxorubicin, and etoposide chemotherapy concurrently with filgrastim. In this population, filgrastim was well tolerated. There was one report of palpable splenomegaly associated with filgrastim therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

Patients with Acute Myeloid Leukemia

Published experience with the administration of filgrastim post-chemotherapy in pediatric patients with AML has included 136 patients. This interim analysis included children receiving intensive induction chemotherapy with filgrastim, and demonstrated that it had no detrimental impact on disease outcome in comparison to a similarly-treated historical control group.

Patients with Severe Chronic Neutropenia

Filgrastim is indicated for chronic administration to adults and pediatric patients with SCN to reduce the incidence and duration of the sequelae of neutropenia. In a phase 3 study, 120 patients with a median age of 12 years (range 1 to 76 years) were treated; 12 of these were infants (1 month to 2 years of age), 47 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age) (see **CLINICAL TRIALS - REFERENCE BIOLOGIC DRUG; INDICATIONS; Monitoring and Laboratory Tests; DOSAGE AND ADMINISTRATION**).

The most commonly reported adverse event in clinical trials was bone pain; splenomegaly has also been reported with chronic administration (see **ADVERSE REACTIONS**). Pediatric patients with congenital types of neutropenia have been reported to develop MDS/AML or cytogenetic abnormalities while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown (see **WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS**).

Other serious long-term risks associated with daily administration of filgrastim have not been identified in pediatric patients (ages 1 month to 17 years) with SCN. Regarding growth and development, long-term follow-up data from the post-marketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of filgrastim treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation, or endocrine function.

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

9. ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Grastofil® to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

9.1 Adverse Reaction Overview

Dose-dependent musculoskeletal pain, specifically medullary bone pain, was the only consistently reported adverse event across all cancer patient populations. These events were usually mild-to-moderate, and most patients that experienced this effect were symptomatically controlled by non-narcotic analgesia.

Bone pain and pain in extremity occurred at a higher incidence in filgrastim-treated patients as compared with placebo-treated patients across all indications.

See **WARNINGS AND PRECAUTIONS** regarding **Splenic Rupture, ARDS, Allergic Reactions** and **Sickle Cell Crises**.

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Cancer Patients Receiving Myelosuppressive Chemotherapy

In clinical trials involving over 350 patients receiving filgrastim following cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase 2 and 3 trials, medullary bone pain, reported in 24% of patients, was the only consistently observed adverse reaction attributed to filgrastim therapy. This bone pain was generally reported to be of mild-to-moderate severity, and could be controlled in most patients with non-narcotic analgesics. Infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20 to 100 µg/kg/day) administered intravenously, and less frequently in patients treated with lower subcutaneous doses of filgrastim (3 to 10 µg/kg/day).

In the randomized, double-blind, placebo-controlled trial of filgrastim therapy following combination chemotherapy in patients (n = 207) with small cell lung cancer, the following adverse events were reported during blinded cycles of study medication (placebo or filgrastim at 4 to 8 µg/kg/day). Events are reported as exposure adjusted since patients remained on double-blind filgrastim a median of 3 cycles versus 1 cycle for placebo.

Table 2: Percentage of Blinded Cycles with Events

Event	Filgrastim Patient Cycles N = 384	Placebo Patient Cycles N = 257
Nausea/Vomiting	57	64
Skeletal Pain	22	11
Alopecia	18	27
Diarrhea	14	23
Neutropenic Fever	13	35

Event	Filgrastim Patient Cycles N = 384	Placebo Patient Cycles N = 257
Mucositis	12	20
Fever	12	11
Fatigue	11	16
Anorexia	9	11
Dyspnea	9	11
Headache	7	9
Cough	6	8
Skin Rash	6	9
Chest Pain	5	6
Generalized weakness	4	7
Sore throat	4	9
Stomatitis	5	10
Constipation	5	10
Pain (Unspecified)	2	7

In this study, there were no serious, life-threatening, or fatal adverse reactions attributed to filgrastim therapy. Specifically, there were no reports of flu-like symptoms, pleuritis, pericarditis, or other major systemic reactions to filgrastim.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase, and alkaline phosphatase occurred in 27% to 58% of 98 patients receiving blinded filgrastim therapy following cytotoxic chemotherapy. Increases were generally mild-to-moderate. Transient decreases in blood pressure (< 90/60 mmHg) which did not require clinical treatment, were reported in 7 of 176 patients in phase 3 clinical studies following administration of filgrastim. No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see **WARNINGS AND PRECAUTIONS, Simultaneous Use with Chemotherapy**).

The safety profile of filgrastim in the pediatric population is comparable to that seen in adult cancer patients receiving cytotoxic chemotherapy. Adverse events considered related to filgrastim administration by the investigators of 3 non-blinded studies included application site disorders, haematologic disorders (including thrombocytopenia), musculoskeletal disorders, and a single case of vasculitis. Of these, musculoskeletal disorders are the most consistent adverse events seen in other filgrastim studies.

Patients with Acute Myeloid Leukemia

In a randomized phase 3 clinical trial involving 521 patients with de novo AML, 259 patients received filgrastim post-chemotherapy and 262 patients received placebo. Filgrastim was generally well tolerated, and most adverse experiences were considered to be the sequelae of the underlying malignancy or cytotoxic chemotherapy. The most frequently reported events were diarrhea, rash, and petechiae, and there were no significant differences between the treatment groups.

Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

In clinical trials with filgrastim, the reported adverse effects were those typically seen in patients receiving intensive chemotherapy followed by bone marrow transplantation. The most common events reported in both control and treatment groups included stomatitis, nausea and vomiting, generally of mild-to-moderate severity and were considered unrelated to filgrastim. In the

randomized studies of BMT involving 167 patients who received study drug, the following events occurred more frequently in patients treated with filgrastim than in controls: nausea (10% vs. 4%), vomiting (7% vs. 3%), hypertension (4% vs. 0%), rash (12% vs. 10%), and peritonitis (2% vs. 0%). None of these events were reported by the investigator to be related to filgrastim. One event of erythema nodosum was reported moderate in severity and possibly related to filgrastim.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

○ Filgrastim Mobilized PBPC Collection

In clinical trials with filgrastim, 126 patients have received filgrastim for mobilization of PBPC. During the mobilization period, adverse events related to filgrastim consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (38%). Headache was reported related to filgrastim in 7% of patients. Mild-to-moderate transient increases in alkaline phosphatase levels were reported related to filgrastim in 21% of the patients who had serum chemistries evaluated during the mobilization phase.

All patients had increases in neutrophil counts consistent with the biological effects of filgrastim. Two patients had a WBC count greater than $100 \times 10^9/L$ with WBC count increases during the mobilization period ranging from $16.7 \times 10^9/L$ to $138 \times 10^9/L$ above baseline. Eighty-eight percent of patients had an increase in WBC count between $10 \times 10^9/L$ and $70 \times 10^9/L$ above baseline. No clinical sequelae were associated with any grade of leukocytosis.

Sixty-five percent of patients had mild-to-moderate anemia and 97% of patients had decreases in platelet counts possibly related to the leukapheresis procedure. Only 5 patients had platelet counts $< 50 \times 10^9/L$.

○ PBPC Transplantation Followed by Filgrastim

During the period of filgrastim administration post PBPC transplant, filgrastim was administered to 110 patients as supportive therapy and adverse events were consistent with those expected after high dose chemotherapy. Mild-to-moderate musculoskeletal pain was the most frequently reported adverse event related to filgrastim reported in 15% of patients.

Patients with Severe Chronic Neutropenia

Mild-to-moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was usually readily controlled with mild analgesics. General musculoskeletal pain was also noted in higher frequency in patients treated with filgrastim. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently and thrombocytopenia ($< 50 \times 10^9/L$) was noted in 12% of patients with palpable spleens. Less than 3% of all patients underwent splenectomy, and most of these had a pre-study history of splenomegaly. Approximately 7% of patients had thrombocytopenia ($< 50 \times 10^9/L$) during filgrastim therapy, most of whom had a pre-study history. In most cases, thrombocytopenia was managed by filgrastim dose reduction or interruption. There were no associated, serious haemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with filgrastim, but was associated with thrombocytopenia in only 2% of patients. Anemia was reported in approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness or concomitant medications.

Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated with filgrastim for SCN (see **WARNINGS AND PRECAUTIONS, *Patients with Severe Chronic Neutropenia***). As of December 31, 1997, data were available from a post-marketing surveillance study of 531 SCN patients with an average follow-up of 4.0 years. Of these 531 patients, 32 were infants (1 month to 2 years of age), 200 were children (2 to 12 years of age), and 68 were adolescents (12 to 16 years of age). Based on analysis of these data, the risk of developing MDS, and AML was confined to the subset of patients with congenital neutropenia (Kostmann's syndrome, congenital agranulocytosis, and Shwachman-Diamond syndrome). A life table analysis of these data revealed that the cumulative risk of developing leukemia or MDS by the end of the eighth year of filgrastim treatment in a patient with congenital neutropenia was 16.5% (95% C.I. = 9.8% to 23.3%); this represents an annual rate of approximately 2%. Leukemic transformation has also been documented in congenital neutropenia patients who have never received filgrastim; it is unknown if the rate of conversion in untreated patients is different from that of treated patients. Cytogenetic abnormalities, including monosomy 7, have been reported in patients treated with filgrastim who had previously documented normal cytogenetic evaluations. It is unknown whether the development of cytogenetic abnormalities, MDS or AML is related to chronic daily filgrastim administration or to the natural history of SCN. Routine monitoring through regular CBCs is recommended for all patients with SCN.

Additionally, annual bone marrow and cytogenetic evaluations are recommended in all patients with congenital neutropenia (see **Monitoring and Laboratory Tests**).

Other adverse events infrequently observed and possible related to filgrastim therapy were: injection site reaction, headache, hepatomegaly, arthralgia, osteoporosis, rash, alopecia, and hematuria/proteinuria.

Patients with HIV Infection

In the multicenter, randomized, controlled trial, 172 of 258 patients were treated with filgrastim which was generally well tolerated. The most frequently reported treatment-related adverse events in the 24-week treatment period were skeletal pain (14.5%), headache (6.4%), back pain and myalgia (5.8% each) and increased alkaline phosphatase (5.2%).

There were no new or unexpected treatment-related events seen in filgrastim-treated patients. Adverse events observed in clinical trials were consistent with progression of HIV disease or events observed in other clinical settings.

There was no apparent increase or decrease in HIV replication and viral load as measured by quantitative reverse transcriptase polymerase chain reaction (RT-PCR). Although prior *in vitro* and *in vivo* studies have not shown any increase in viral load following use of filgrastim in HIV-infected patients. The randomized study was not powered to address this issue and the possibility of an effect due to filgrastim on HIV replication cannot be entirely excluded.

As of 31 January 1996, an estimated 1.2 million patients worldwide have received filgrastim therapy across all indications. Of an estimated 150,000 HIV-infected patients receiving filgrastim to date, there have been 106 spontaneous adverse event reports received worldwide. No new adverse event patterns were identified in adults or children receiving filgrastim for neutropenia associated with HIV infection. Five deaths were reported in 106 post-marketing reports in patients receiving filgrastim for HIV infection. Three of 5 deaths were attributed to various manifestations of HIV disease progression. In the fourth case, the cause of death was not reported. In the fifth case, the physician reported that death in the context of ARDS occurred in the absence of fever and microbiological cause and was typical of bleomycin pulmonary toxicity.

However, the physician reported that this may have been enhanced by filgrastim. It is notable, however, that randomized trials, and non-randomized trials demonstrated no increase in the known pulmonary toxicity of bleomycin when filgrastim was added to treatment.

In the randomized controlled study with filgrastim, the overall incidence of thrombocytopenia was 9.9% in the filgrastim-treated groups compared with 8.1% in the control group. Severe thrombocytopenia occurred in 7% of the filgrastim-treated patients and 3.5% of control patients in the controlled, randomized study. During this study, mean platelet count decreased at week 2 in the filgrastim-treated patients, but returned to baseline by week 3 and remained stable thereafter. In the post-marketing experience of HIV-infected patients which includes an estimated 150,000 patients worldwide, 10 of 106 spontaneous reports of adverse reactions were for thrombocytopenia. Of these, 3 cases were reported as serious.

Because adverse events of thrombocytopenia in HIV-infected individuals are multifactorial and may be attributed to the natural progression of HIV disease and associated infections, and because of the inconsistent occurrence of thrombocytopenia in a small number of patients in the aforementioned clinical trials, no definitive relationship between filgrastim therapy in HIV-infected patients and thrombocytopenia can be established.

In one study, 16 of 24 patients (66.7%) were reported to have splenomegaly during an observation period of 49-701 days. However, no baseline measurements of spleen size were made for comparison to on-study values. In 3 other uncontrolled trials, only 1 of 297 patients (0.3%) had a report of splenomegaly. Since splenomegaly is a common clinical finding in 72% of patients with AIDS sometime during the course of their disease, it is likely that the observed splenomegaly was associated with HIV disease and not related to filgrastim.

Clinical Experience Relevant to all Indications

In combined clinical trials involving a total of 1834 patients, the following adverse reactions which are not presented in the adverse reaction sections by indication above, occurred with $\geq 5\%$ higher incidence in filgrastim treated patients compared to controls: oropharyngeal pain, decreased appetite, oral pain, malaise, edema peripheral, sepsis, bronchitis, upper respiratory tract infection, urinary tract infection, muscle spasms, dizziness, hypoesthesia, insomnia, hypersensitivity, hemoglobin decreased, rash maculo-papular and transfusion reaction.

9.3 Less Common Clinical Trial Adverse Reactions

Not available in the reference biologic drug labelling.

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not available in the reference biologic drug labelling.

9.5 Clinical Trial Adverse Reactions (Pediatrics)

Please refer to Section **8.1.3 Pediatrics** for results of studies in pediatric patients with the reference product Neupogen.

9.6 Post-Market Adverse Reactions

In addition to the events listed above, reports of serious adverse reactions have been identified post-market in patients receiving filgrastim, including:

- Splenomegaly (enlarged spleen) and splenic rupture (see **WARNINGS AND PRECAUTIONS: Splenic Rupture**)
- Acute respiratory distress syndrome (ARDS) (see **WARNINGS AND PRECAUTIONS: Respiratory**)
- Alveolar hemorrhage (manifesting as pulmonary infiltrates and hemoptysis) (see **WARNINGS AND PRECAUTIONS: Respiratory**)
- Allergic reactions, including anaphylactic reactions (see **WARNINGS AND PRECAUTIONS: Hypersensitivity/Allergic Reactions**)
- Sickle cell crisis (see **WARNINGS AND PRECAUTIONS: Hematologic**)
- Cutaneous vasculitis (see **WARNINGS AND PRECAUTIONS: Cutaneous Vasculitis**)
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Chondrocalcinosis pyrophosphate (in patients treated for cancer)
- Decreased bone density and osteoporosis (in pediatric patients with SCN receiving chronic treatment with filgrastim)
- Capillary Leak Syndrome (see **WARNINGS AND PRECAUTIONS: Capillary Leak Syndrome**)
- Leukocytosis (see **WARNINGS AND PRECAUTIONS: Leukocytosis**)
- Bone Pain
- Glomerulonephritis (see **WARNINGS AND PRECAUTIONS: Glomerulonephritis**)

10. DRUG INTERACTIONS

10.1 Serious Drug Interactions Box

Not Applicable

10.2 Overview

Interactions of filgrastim with other cytokines, including haematopoietic growth factors, have been observed in animal studies. The safety, efficacy, and possible interactions of filgrastim used in combination with other cytokines have not been characterized in clinical trials. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

10.3 Drug-Drug Interactions

Interactions with other drugs have not been established.

10.4 Drug-Food Interactions

Interactions with food have not been established.

10.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.6 Drug-Laboratory Test Interactions

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

11. ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Filgrastim is a human granulocyte colony stimulating factor (G-CSF) produced by recombinant DNA technology. G-CSF regulates the production of neutrophils within the bone marrow; endogenous G-CSF is a glycoprotein produced by monocytes, fibroblasts, and endothelial cells. G-CSF is a colony stimulating factor which has been shown to have minimal direct *in vivo* or *in vitro* effects on the production of other haematopoietic cell types. Grastofil[®] (filgrastim) is the name for recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).

11.2 Pharmacodynamics

In phase 1 studies involving 96 patients with various non-myeloid malignancies, filgrastim administration resulted in a dose-dependent increase in neutrophil counts over the dose range of 1 to 70 µg/kg/day. This increase in neutrophil counts was observed whether filgrastim was administered intravenously (1 to 70 µg/kg twice daily), subcutaneously (1 to 3 µg/kg once daily), or by continuous subcutaneous infusion (3 to 11 µg/kg/day). With discontinuation of filgrastim therapy, neutrophil counts returned to baseline, in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic [measured by migration under agarose using N-formylmethionyl-leucyl-phenylalanine (fMLP) as the chemotaxin] activity *in vitro*.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving filgrastim, however, the percentage of monocytes in the differential count remained within the normal range. In all studies to date, absolute counts of both eosinophils and basophils did not change and were within the normal range following administration of filgrastim. Increases in lymphocyte counts following filgrastim administration have been reported in some normal subjects and cancer patients.

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. In addition, Dohle bodies, increased granulocyte granulation, as well as hypersegmented neutrophils have been observed. Such changes were transient, and were not associated with clinical sequelae nor were they necessarily associated with infection.

11.3 Pharmacokinetics

Information generated and published by independent investigators suggests that filgrastim binds to the G-CSF receptor (G-CSFR) on the surface of the neutrophils, and the drug-receptor complex is internalized to the endosomal compartments, and either recycled or degraded; the receptor-mediated processes appear to be an important mode of disposition (elimination) for

filgrastim. In general, linear and nonlinear filgrastim pharmacokinetics may be observed in relation to the receptor-mediated disposition and this involves the filgrastim serum concentration, changes in cell number precursors and circulating neutrophils – complex manifestations which also relate to the filgrastim dosage regimen and the biological effects upon multiple doses.

Over the wide range of doses of filgrastim examined (3.45 – 69.0 µg/kg) in the early clinical trials for filgrastim, absorption and clearance, in general, approximated first-order pharmacokinetics, showing an apparent positive linear correlation between the parenteral dose and both the serum concentration and area under the concentration-time curves. Continuous intravenous infusion of 20 µg/kg of filgrastim over 24 hours resulted in mean and median serum concentrations of approximately 48 and 56 ng/mL, respectively.

Subcutaneous administration of 3.45 µg/kg and 11.5 µg/kg resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. The volume of distribution averaged 150 mL/kg in normal subjects and cancer patients. The elimination half-life, in both normal subjects and cancer patients, was approximately 3.5 hours. Clearance rates of filgrastim were approximately 0.5 to 0.7 mL/min/kg. Single parenteral doses or daily intravenous doses, over a 14 day period, resulted in comparable half-lives. The half-lives were similar for intravenous administration (231 minutes, following filgrastim doses of 34.5 µg/kg) and for subcutaneous administration (210 minutes, following filgrastim doses of 3.45 µg/kg). Continuous 24-hour intravenous infusions of 20 µg/kg over an 11 to 20 day period produced steady state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated.

Special Populations and Conditions

Pediatrics: In a study of 15 children with neuroblastoma, 5 children were treated at each of the 3 dose levels; 5, 10, and 15 µg/kg/day filgrastim subcutaneously for 10 days. Peak concentrations of filgrastim of 3 to 117 ng/mL were reached after 4 to 12 hours with measurable filgrastim concentrations for the entire 24-hour dosing interval. Mean elimination half-life of 5.8 hours and 4.5 hours were found on day 1 and on day 10, respectively.

Geriatrics: Pharmacokinetic data in geriatric patients (> 65 years) are not available.

12. STORAGE, STABILITY, AND DISPOSAL

Grastofil® (filgrastim) should be stored in the refrigerator at 2 °C to 8°C.

Accidental one-time exposure to temperatures up to 30°C or exposure to freezing temperatures (less than 0°C) does not adversely affect the stability of Grastofil®. If exposure has been greater than 24 hours or frozen more than once, then Grastofil® should not be used.

Within its shelf-life and for the purpose of ambulatory use, the patient may remove Grastofil® from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 15 days. At the end of this period, Grastofil® should not be put back in the refrigerator and should be disposed of in accordance with local requirements.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The pre-filled syringe should be disposed of by placing the entire pre-filled syringe with guard activated into an approved puncture-proof container.

13. SPECIAL HANDLING INSTRUCTIONS

Grastofil® (filgrastim) should not be vigorously shaken. Do not freeze. Store in the carton provided to protect from light.

PART II: SCIENTIFIC INFORMATION

14. PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Filgrastim
Chemical name:	Recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF)
Molecular formula and molecular mass:	$C_{845}H_{1339}N_{223}O_{243}S_9$ Filgrastim consists of 175 amino acids with a molecular weight 18,800 Daltons
Structural formula:	Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by <i>Escherichia coli</i> (<i>E. coli</i>) bacteria into which has been inserted the human granulocyte colony stimulating factor gene. Filgrastim has a molecular weight of 18,800 Daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA analysis, except for the addition of an N-terminal methionine necessary for expression of <i>E.coli</i> . Because filgrastim is produced in <i>E.coli</i> , the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.
Physicochemical properties:	Filgrastim drug substance is a clear and colourless liquid with a pH of 4.0 ± 0.2 .

Product Characteristics

Grastofil[®] (filgrastim) is a sterile, clear, colourless, preservative-free liquid.

15. COMPARATIVE CLINICAL TRIALS

15.1 Trial Design and Study Demographics

Three comparative pharmacokinetic (PK)/ pharmacodynamic (PD) phase 1 studies were conducted in 187 healthy volunteers (147 received Grastofil[®]) to support similarity between Grastofil[®] and the reference biologic drug (Neupogen).

- KWI-300-101 was a single-dose, randomized, double-blind, two-way cross-over study in healthy volunteers to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Grastofil[®] and the reference product. Single doses of Grastofil[®] 5 µg/kg (300 µg/0.5 mL) or Neupogen 5 µg/kg (480 µg/0.5 mL) were given intravenously.

- KWI-300-102 was a single-dose, randomized, double-blind, two-way cross-over study in healthy volunteers to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Grastofil® and the reference product. Single subcutaneous doses of Grastofil® 75 µg and 150 µg (300 µg/0.5 mL), or Neupogen 75 µg and 150 µg (300 µg/0.5 mL) were given. The PK parameters were assessed only at the 150 µg dose and the results are summarized in Table 5.
- KWI-300-103 was a repeat dose, randomized, double-masked, active and placebo-controlled, parallel group study in healthy volunteers to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Grastofil® and the reference product. Subcutaneous doses of Grastofil® or Neupogen 5 µg/kg/per day (480 µg/0.5 mL) for 4 days, or Placebo (physiological NaCl 0.9%, 0.5 mL/day) for 4 days, were given.

In addition, a non-comparative single arm safety study in breast cancer patients (Study KWI-300-104) was conducted in patients with Stage IIA, IIB, or IIIA breast cancer, undergoing TAC chemotherapy treatment in an adjuvant setting of which 120 patients received Grastofil®.

An overview of the study design and demographic characteristics of patients enrolled in each clinical study are presented in Table 3.

Table 3: Grastofil® Clinical Studies – Summary of trial design and patient demographics

Study	Trial Design	Dosage, route of administration	Duration	Study subjects (n)	Median age (range)	Sex n (%)
KWI-300-101	Phase 1, single-dose, randomized, double-blind, two-way cross-over study - PK and PD evaluation of Grastofil® and Neupogen in healthy volunteers	Grastofil® 5 µg/kg (300 µg/0.5 mL in single-use prefilled syringes), intravenous Neupogen 5 µg/kg (480 µg/0.5 mL in single-use prefilled syringes), intravenous	~45 days	36	30 (19-43)	18 (50%) Male 18 (50%) Female
KWI-300-102	Phase 1, single-dose, randomized, double-blind, two-way cross-over study, dose response - PK and PD evaluation of Grastofil and Neupogen® in healthy volunteers	Grastofil® 75 µg and 150 µg (300 µg/0.5 mL in single-use prefilled syringes), subcutaneous Neupogen 75 µg and 150 µg (300 µg/0.5 mL in single-use prefilled syringes), subcutaneous	~45 days	73	26 (19-52)	48 (66%) Male 25 (34%) Female
KWI-300-103	Phase 1, randomized, double-masked, active and placebo-controlled, parallel	Grastofil® 5 µg/kg/per day for 4 days (480 µg filgrastim / 0.5 mL in single-use prefilled syringes);	~20 days	78	26 (18 – 48)	38 (49%) Male 40 (51%) Female

Study	Trial Design	Dosage, route of administration	Duration	Study subjects (n)	Median age (range)	Sex n (%)
	group study to examine the PD of repeat dose Grastofil® and Neupogen in healthy volunteers	subcutaneous Neupogen 5 µg/kg/per day for 4 days (480 µg filgrastim / 0.5 mL in single-use prefilled syringes); subcutaneous Placebo; physiological NaCl 0.9%, 0.5 mL per day for 4 days; subcutaneous				
KWI-300-104	Phase 3, non-comparative, multicentre, repeat dose safety study with Grastofil® in breast cancer patients receiving TAC chemotherapy as routine treatment	Grastofil® 5 µg/kg/per day (300 µg or 480 µg filgrastim / 0.5 mL in single-use prefilled syringes), administered daily for a maximum up to study cycle Day 15, subcutaneous	~ 51 weeks	120	50 (28 – 68)	120 (100%) Female

15.2 Comparative Study Results

15.2.1 Comparative Bioavailability Studies

In the three phase 1 studies described below, the Per Protocol (PP) population was defined as the population set that included all randomized subjects without any major protocol deviations. This population was considered to be the primary analysis population for both pharmacokinetics and pharmacodynamics assessment.

15.2.1.1 Pharmacokinetics

Study KWI-300-101

The PK parameters for Study KWI-300-101 are summarized in Table 4.

Table 4: Mean Pharmacokinetic Parameters of the Per Protocol (PP) Population Following a Single Intravenous Infusion of 5 µg/kg Grastofil® or Neupogen to Healthy Volunteers (Study KWI-300-101)

Endpoint		Grastofil® (N = 35)	Neupogen (N = 35)	Ratio of Geometric Means [%] ^b
AUC _T [min*ng/mL]	Mean (SD)	22047 (4060)	24341 (4530)	90.6

C _{max} [ng/mL]	Mean (SD)	103 (15)	112 (16)	92.5
T _{1/2} [min] ^a	Mean (SD)	410 (84)	388 (113)	
T _{max} [min]	Mean (SD)	16.3 (9.1)	16.0 (5.5)	
Clearance (mL/min)	Mean (SD)	16.4 (4.1)	14.9 (3.7)	
Volume of Distribution (mL)	Mean (SD)	9875 (4003)	8575 (4241)	

AUC_T = Area under the concentration-time curve from 0 hours up to 32 hours following filgrastim administration;

C_{max} = Maximum plasma concentration; T_{1/2} = Terminal half-life; T_{max} = Time at which C_{max} is achieved;

SD = Standard Deviation; Clearance = Systemic Clearance; Volume of distribution, based on AUC(0-∞)

^a = Terminal half-life was obtained based on blood sampling of up to 32 hours post-dose

^b = The ratio of geometric means is the ratio (Grastofil[®]/Neupogen) of the inverse transformation of the least square means.

In study KWI-300-101, of the 36 subjects that were randomized and dosed in the study, one subject had a positive pregnancy test on day 5 therefore; the second dose was not administered. This patient was excluded from the PP population, and hence a total of 35 subjects were included in the PP population.

Study KWI-300-102

The PK parameters for KWI-300-102 were assessed only at the 150 µg dose and the results are summarized in Table 5.

Table 5: Mean (SD) Pharmacokinetic Parameters of the PP Population Following a Single Subcutaneous Injection of 150 µg Grastofil[®] or Neupogen in Healthy Volunteers (Study KWI-300-102)

Endpoint		Grastofil [®] 150 µg (N = 35)	Neupogen 150 µg (N = 35)	Ratio of Geometric Means [%] ^b	90% CI[%]
AUC _T [min*ng/mL]	Mean (SD)	3276 (920)	3415 (1094)	96.8	91.0-103.0
C _{max} [ng/mL]	Mean (SD)	7.72 (2.35)	8.35 (3.05)	94.6	85.9-104.1
T _{1/2} [min] ^a	Mean (SD)	519 (154)	551 (197)		
T _{max} [min]	Mean (SD)	279 (42)	284 (54)		

AUC_T = Area under the concentration-time curve from 0 hours up to 72 hours following filgrastim administration; C_{max} = Maximum plasma concentration; T_{1/2} = Terminal elimination half-life; T_{max} = Time at which C_{max} is achieved; SD = Standard Deviation; CI = Confidence interval

^a = Terminal half-life was obtained based on blood sampling of up to 72 hours post-dose

^b = The ratio of geometric means is the ratio (Grastofil[®]/Neupogen) of the inverse transformation of the least square means.

In study KWI-300-102, of the 73 subjects who were randomized and dosed (36 subjects in the 150 µg dose cohort and 37 subjects in the 75 µg dose cohort), 5 subjects were excluded from the PP population; 4 subjects from the 75 µg dose cohort and 1 subject from the 150 µg dose cohort, and hence 68 subjects were included in the PP population (35 subjects in the 150 µg dose cohort, and 33 subjects in the 75 µg dose cohort). The reasons for exclusion included adverse event (infection) in 2 subjects, missing ANC value at study day 8 in 2 subjects and voluntary withdrawal of consent for 1 subject.

Study KWI-300-103

The PK parameters for Study KWI-300-103 are summarized in Table 6.

Table 6: Mean (SD) Pharmacokinetic Parameters of the PP Population Following a Single and Four Daily Subcutaneous Injections of 5 µg/kg Grastofil® or Neupogen in Healthy Volunteers (Study KWI-300-103)

Endpoint		Grastofil® (N = 35)	Neupogen (N = 34)	Ratio of Geometric Means [%] ^b	90% CI [%]
AUC _T [min*ng/mL] Day 1	Mean (SD)	11735 (2737)	11839 (3292)	100.2	90.3-111.1
AUC _{ss} [min*ng/mL] Day 4	Mean (SD)	5441 (1485)	5388 (1790)	102.3	91.1-114.9
C _{max} [ng/mL] Day 1	Mean (SD)	25.9 (7.0)	25.5 (7.8)	102.2	91.3-114.5
T _{1/2} [min] ^a Day 1	Mean (SD)	216 (48)	207 (39)		
T _{max} [min] Day 1	Mean (SD)	297 (35)	307 (33)		

AUC_T = Area under the concentration-time curve from 0 hours up to 24 hours following filgrastim administration;
AUC_{ss} = Area under the plasma concentration-time curve in steady state, following the last filgrastim administration (trial day 4) up to the last measured filgrastim concentration; C_{max} = Maximum plasma concentration;

T_{1/2} = Terminal half-life; T_{max} = Time at which C_{max} is achieved; SD = Standard Deviation; CI = Confidence interval
^a = Terminal half-life was obtained based on blood sampling of up to 24 hours post-dose

^b = The ratio of geometric means is the ratio (Grastofil®/Neupogen) of the inverse transformation of the least square means.

In study KWI-300-103, of the 78 healthy subjects who were randomized and dosed, 3 subjects were excluded from the PP population, and hence 75 subjects were included in the PP population (35 subjects receiving Grastofil®, 34 subjects receiving Neupogen and 6 subjects receiving placebo). The reasons for exclusion included adverse event (infection) in 2 subjects and voluntary subject withdrawal prior to Day 4 for 1 subject.

15.2.1.2 Pharmacodynamics

Study KWI-300-101

The PD results for Study KWI-300-101 are summarized in Table 7.

The absolute neutrophil count (ANC) C_{max} and AUC were assessed as pharmacodynamic endpoint parameters following the administration of Grastofil[®] and Neupogen. The results demonstrated similarity of Grastofil[®] and Neupogen with regards to the PD variables ANC C_{max} and ANC AUC₍₀₋₇₂₎ after single i.v. infusion of 5 µg/kg (Table 7). In both treatment groups, ANC increased as expected after i.v. infusion, reached a maximum after 12 hours, and then decreased towards baseline values by 72 hours post-dose.

Table 7: Pharmacodynamic Parameters of the PP Population Following a Single Intravenous Infusion of 5 µg/kg Grastofil[®] or Neupogen to Healthy Volunteers (Study KWI-300-101)

Endpoint		Grastofil [®] (N = 35)	Neupogen (N = 35)	Ratio of Geometric Means [%] ^a	95% CI [%]
ANC C_{max} [cells × 10 ⁹ /L]	Mean (SD)	19.0 (4.4)	19.3 (5.2)	99.5	92.5 -107.1
ANC AUC _{0-72h} [min*cells × 10 ⁹ /L]	Mean (SD)	46137 (8608)	46602 (9322)	99.1	94.8 – 103.7

ANC = Absolute neutrophil count; C_{max} = Maximum observed ANC over the sampling interval;
AUC₀₋₇₂ = The area under the curve (calculated by the linear trapezoidal rule) from time zero measured up to 72 hours; SD = Standard Deviation; CI = Confidence interval

^a = The ratio of geometric means is the ratio (Grastofil[®]/Neupogen) of the inverse transformation of the least square means.

Study KWI-300-102

The PD results for KWI-300-102 are summarized in Table 8 and Table 9.

The absolute neutrophil count (ANC) C_{max} and AUC were assessed as pharmacodynamic endpoint parameters following the administration of Grastofil[®] and Neupogen. The results demonstrated similarity of Grastofil[®] and Neupogen with regards to the PD variables ANC C_{max} and ANC AUC₍₀₋₇₂₎ after single s.c. injection of Grastofil[®] 150 µg and 75 µg or Neupogen 150 µg and 75 µg (Table 8 and Table 9). In both treatment groups, the ANC increased as expected after s.c. injection for both dose levels of 150 µg and 75 µg, reached a maximum around 12 hours, and then decreased to near baseline values by 72 hours post-dose.

Table 8: Pharmacodynamic Parameters of the PP Population Following a Single Subcutaneous Injection of 75 µg Grastofil® or Neupogen to Healthy Volunteers (Study KWI-300-102)

Endpoint		Grastofil® 75 µg (N = 33)	Neupogen 75 µg (N = 33)	Ratio of Geometric Means [%] ^a	95% CI [%]
ANC C _{max} [cells × 10 ⁹ /L]	Mean (SD)	17.1 (3.7)	18.6 (4.1)	92.0	87.1 – 97.1
ANC AUC _{0-72h} [min*cells × 10 ⁹ /L]	Mean (SD)	35077 (6526)	37010 (7623)	95.0	91.1 – 99.0

ANC = Absolute neutrophil count; C_{max} = Maximum observed ANC over the sampling interval;
AUC₀₋₇₂ = The area under the curve (calculated by the linear trapezoidal rule) from time zero measured up to 72 hours; SD = Standard Deviation; CI = Confidence interval

^a = The ratio of geometric means is the ratio (Grastofil®/Neupogen) of the inverse transformation of the least square means.

Table 9: Pharmacodynamic Parameters of the PP Population Following a Single Subcutaneous Injection of 150 µg Grastofil® or Neupogen to Healthy Volunteers (Study KWI-300-102)

Endpoint		Grastofil® 150 µg (N = 35)	Neupogen 150 µg (N = 35)	Ratio of Geometric Means [%] ^a	95% CI [%]
ANC C _{max} [cells × 10 ⁹ /L]	Mean (SD)	19.0 (3.8)	19.6 (3.3)	96.3	91.02 – 101.93
ANC AUC _{0-72h} [min*cells × 10 ⁹ /L]	Mean (SD)	43209 (7922)	43980 (6866)	97.7	92.97 – 102.64

ANC = Absolute neutrophil count; C_{max} = Maximum observed ANC over the sampling interval;
AUC₀₋₇₂ = The area under the curve (calculated by the linear trapezoidal rule) from time zero measured up to 72 hours; SD = Standard Deviation; CI = Confidence interval

^a = The ratio of geometric means is the ratio (Grastofil®/Neupogen) of the inverse transformation of the least square means.

Study KWI-300-103

The PD results for Study KWI-300-103 are summarized in Table 10.

The absolute neutrophil count (ANC) C_{max} and AUC were assessed as pharmacodynamic endpoint parameters following the administration of Grastofil® and Neupogen. The results demonstrated similarity of Grastofil® and Neupogen with regard to PD variables after single and repeat s.c. administration of doses of 5 µg/kg (Table 10). In both active treatment groups, mean ANC increased as expected after s.c. injection, reached a maximum around 12 hours, and then decreased thereafter on trial day 1. Similar patterns but with higher levels were observed on day 4. The ANC C_{max} was increased by about 45% from day 1 to day 4 for both products. In the placebo group, mean ANC remained at the baseline level throughout the day as expected for both trial days.

Table 10: Pharmacodynamic Parameters of the PP Population Following Four Daily S.C. Injections of 5 µg/kg Grastofil® or Neupogen to Healthy Volunteers (Study KWI-300-103)

Endpoint		Grastofil® (N = 35)	Neupogen (N = 34)	Placebo (N = 6)	Ratio of Geometric Means [%] ^a	95% CI [%]
ANC C _{max} (0-96h) [cells × 10 ⁹ /L]	Mean (SD)	30.5 (6.2)	32.3 (7.7)	4.14 (0.63)	95.2	85.8 – 105.6
ANC AUC _{0-96h} [min*cells × 10 ⁹ /L]	Mean (SD)	114232 (19346)	119436 (20700)	ND	95.6	88.0 – 103.8

ANC = Absolute neutrophil count; C_{max} = Maximum observed ANC over the sampling interval;

AUC_{0-96h} = Area under the concentration-time curve from 0 hours up to 96 hours following the first filgrastim administration; SD = Standard Deviation; CI = Confidence interval, ND = Not Determined

^a = The ratio of geometric means is the ratio (Grastofil®/Neupogen) of the inverse transformation of the least square means.

In KWI-300-103, absolute CD34+ cell count was also assessed on study days 1 (i.e., Baseline) and 5 (after 4 treatment doses). The mean CD34+ cell counts were 2.00 ± 0.80/µL for Grastofil® and 1.86 ± 0.75 /µL for Neupogen at baseline. Grastofil® increased CD34+ cell counts to 27.65 ± 16.54 /µL and Neupogen increased CD34+ counts to 24.48 ± 14.98 /µL on day 5. For the placebo group, the mean CD34+ cell counts were similar on day 1 and day 5 (2.34 ± 0.70 /µL vs. 2.56 ± 0.78 /µL).

15.2.2 Comparative Safety and Efficacy

Non-Comparative Single-Arm Safety Study - Study KWI-300-104

KWI-300-104 was a single-arm, multicenter, repeat dose safety study of Grastofil® (5 µg/kg/day, subcutaneous) in female patients, with stage IIA, IIB or IIIA breast cancer receiving TAC chemotherapy (docetaxel 75 mg/m² i.v., doxorubicin 50 mg/m² i.v., and cyclophosphamide 500 mg/m² i.v.) known to induce neutropenia. The study consisted of 3 treatment periods: screening (up to 3 weeks), treatment period (6 cycles, 3 weeks between each treatment cycle) and safety follow-up period (up to 30 weeks following completion of TAC chemotherapy). During the treatment period, treatment with Grastofil® began on day 2 of every chemotherapy cycle (at least 24 hours after chemotherapy) and was continued up to 14 days or until post-nadir absolute neutrophil count (ANC) recovery to normal or near-normal values by laboratory standards, whichever occurred first.

The patient population consisted of 120 Caucasian female patients with a mean age of 49.97 (SD: 9.52) and range of 28 – 68 years, with stage IIA, IIB or IIIA breast cancer without neoadjuvant chemotherapy for this breast cancer. There were 39 (32.50%) patients at tumour stage IIA, 44 (36.67%) at stage IIB and 37 (30.83%) at stage IIIA. All patients were chemotherapy naïve and 22 (18.3%) patients had prior radiotherapy. The mean body weight was 71.1 kg, mean body height was 163.4 cm and mean BMI was 26.7 kg/m².

In study KWI-300-104, 120 subjects were dosed. Overall, 113 patients (94.17%) completed the treatment period, 109 (90.83%) completed the Safety Follow-up period and 11 patients (9.17%) prematurely discontinued the study.

The types, frequencies and severity of adverse events were comparable between Grastofil® and the reference biologic drug in the three comparative PK/PD studies in healthy volunteers.

15.2.2.1 Immunogenicity

A summary of the immunogenicity results in the single arm study in breast cancer patients (KWI-300-104) are presented below.

For KWI-300-104 with Grastofil®, immunogenicity samplings were performed throughout in order to monitor the development of anti-drug antibodies in the patients. Immunogenicity baseline samples were taken before the initiation of each cycle in immunosuppressed state (when receiving chemotherapy) and thereafter in the safety follow-up phase in weeks 20, 24, 36 and 48 relative to the first chemotherapy treatment. There were no signs of immunogenicity either detected by the laboratory or by clinical observation. Antibodies were detected only in the Screening antibody assay in 4 patients (9 samples). None of the samples were confirmed as positive in the Confirmatory assay.

In addition, there were no clinical manifestations of antibody formation, such as either hypersensitivity reactions or decreased ANC after completion of the treatment period.

15.2.2.2 Authorized Indications

Grastofil® (filgrastim) is indicated for the following:

- cancer patients receiving myelosuppressive chemotherapy,
- patients with acute myeloid leukemia,
- cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation,
- cancer patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy,
- patients with severe chronic neutropenia (SCN),
- patients with HIV infection.

There are no clinical trials conducted with Grastofil® in the following patient populations:

- acute myeloid leukemia,
- cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation,
- cancer patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy,
- severe chronic neutropenia and HIV infection.

Grastofil® has not been studied in pediatrics.

The use of Grastofil® in the above indications is supported in consideration of the demonstrated similarity of product quality characteristics, non-clinical, human pharmacokinetic and pharmacodynamics between Grastofil® and the reference product as well as a safety study in breast cancer patients receiving Grastofil®.

16. COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

16.1 Comparative Non-Clinical Pharmacodynamics

In vitro and *In vivo* Studies

The mechanism of action of filgrastim is specified by the binding of the molecule to a Granulocyte Colony Stimulating Factor Receptor (G-CSFR) on the surface of neutrophils. The G-CSFR is thereby activated, resulting in a proliferation of granulocytes. This phenomenon can be studied *in vitro* by G-CSFR binding and cell proliferation assays. G-CSFR binding is studied by flow cytometry which measures the binding of filgrastim to the G-CSFR on the surface of whole cells (neutrophils isolated from whole blood). The *in vitro* cell proliferation (potency) assay measures the ability of filgrastim to stimulate proliferation of a G-CSF responsive murine cell line. The comparative pharmacodynamics of Grastofil[®] versus Neupogen was also assessed *in vivo* in neutropenic female Balb/c mice and in Swiss Albino mice for the restoration of absolute neutrophil counts. The findings of these *in vitro* and *in vivo* tests are summarized in Table 11.

Table 11: Summary of *in vitro* and *in vivo* Studies Comparing Pharmacodynamic Activity of Grastofil[®] and Neupogen

Test Method	Key Findings
Comparative binding of Grastofil [®] and Neupogen to the G-CSFR by flow cytometry	Relative binding affinities of Grastofil [®] and Neupogen to cell-surface G-CSFR were shown to be comparable
Comparative cell proliferation of Grastofil [®] and Neupogen by <i>in vitro</i> potency assay	Relative potencies of Grastofil [®] and Neupogen were shown to be comparable
Restoration of neutrophil cell counts by Grastofil [®] and Neupogen in neutropenic female balb/c mice	Restoration of absolute neutrophil counts was comparable in neutropenic mice treated with Grastofil [®] and Neupogen.
<i>In-vivo</i> bioassay for GCSF in neutropenic Swiss Albino male mice for the restoration of absolute neutrophil counts	Restoration of absolute neutrophil counts was comparable in neutropenic mice treated with Grastofil [®] and Neupogen.

16.2 Comparative Toxicology

A repeat-dose toxicity study was performed in Wistar rats to assess the safety and toxicity of subcutaneously administered Grastofil[®] in comparison to Neupogen. This 28-day sub-acute study also included comparative toxicokinetic assessment after single and daily subcutaneous and intravenous administration of Grastofil[®] and Neupogen, over a period of 14 days. In addition, a comparative local tolerance study was conducted to compare the irritation potential of Grastofil[®] and Neupogen as shown in Table 12.

Table 12: Summary of Comparative Repeat-Dose Toxicity with Grastofil[®] and Neupogen

Study ID		Species/Gender (Number)/Group	Dose/Route/Duration	Major Findings
259.120.897	Repeat-dose Toxicity	Wistar rats/ M (10) and F (10)/ Grastofil [®] and Neupogen	50,150 and 500 µg/kg b.w. Grastofil [®] 150 µg/kg b.w. Neupogen daily s.c administration/28-days	No major toxicity; Grastofil [®] was found comparable to Neupogen in toxicity profile, pharmacological assessment and immunogenicity potential.
	Toxicokinetics	Wistar rats/M (10) and F (10)/ Grastofil [®] and Neupogen	50, 150 and 500 µg/kg b.w. Grastofil [®] 50 and 500 µg/kg b.w. Neupogen Single s.c and i.v. administration and repeated s.c. and i.v. administration /14-days	No major toxicity; Grastofil [®] was found comparable to Neupogen in toxicokinetic profile
410.143.1501	Local Tolerance	New Zealand rabbits/M(3)/ Grastofil [®] and Neupogen	480 µg Grastofil [®] per 0.5 mL acetate buffer 480 µg Neupogen per 0.5 mL acetate buffer p.v. and i.m. administration/4 days	No local tolerance toxicity and irritation potential in Grastofil [®] and Neupogen

b.w.= body weight, F= female, i.m.= intramuscular, i.v.= intravenous, M = male, p.v.= paravenous, s.c.= subcutaneous

Study 259.120.897 was a GLP study which included the toxicity, toxicokinetics, and immunogenicity assessment of Grastofil[®] in comparison to Neupogen. In addition, pharmacological parameters (haematological assessment for increase in the Absolute Neutrophil Counts) were also assessed. The effects of Grastofil[®] and Neupogen with respect to the toxicity and pharmacological profile were assessed at the mid-dose of 150 µg/kg body weight which was expected to be the most sensitive dose for the comparison of similarity. The toxicokinetic measurement compared serum concentration of Grastofil[®] and Neupogen for the pharmacokinetic parameters of AUC, C_{max}, AUC_{last}, T_{1/2}, V_{obz}, and CL_{obz}, respectively.

All animals from the Grastofil[®] and Neupogen treatment groups survived until scheduled necropsy in the repeat-dose toxicity assessment. Body weight gain and food consumption was comparable between the treatment groups of Grastofil[®] and Neupogen. Clinical findings were comparable in the mid-dose groups of Grastofil[®] and Neupogen treated animals with swelling of the hind legs or only the joints of the hind legs. Associated findings were a relieving posture or paralysis of the hind legs.

Animals dosed with Grastofil[®] as well as with Neupogen showed an increase in alkaline phosphatase levels and in spleen weight, with both these effects being dose dependent. The change in spleen weight was accompanied by histiocytosis frequently combined with an increased hemopoiesis, observed in both, in Grastofil[®] and the Neupogen treated animals. A thickening of spleen capsule due to a fibrosis was also observed in the Grastofil[®] and Neupogen treated animals. Swelling of the hind limbs or the joints of the hind legs were observed in all dose groups when compared to the control group.

Immunogenicity analysis showed that a biologically relevant antibody response was not present in the animals treated with Grastofil® or Neupogen. No effect of Grastofil® or Neupogen was observed on serum levels of IgG or IgM in all treatment groups. A dose-dependent increase in white blood cells, in particular in neutrophils, was found with both, Grastofil® and Neupogen. No difference was observed between Grastofil® and Neupogen with regard to the efficacy of the administered treatment. With regards to the toxicokinetic assessment, there were no significant differences observed in the toxicokinetic profile of Grastofil® and Neupogen after single and repeated intravenous administrations. In addition, both the single and repeat-dose administrations by the intravenous and subcutaneous routes of administration resulted in a dose-linear exposure.

Local tolerance and irritation potential of Grastofil® was comparatively assessed versus Neupogen in a GLP complaint Study 410.143.1501 conducted in male New Zealand White rabbits via the paravenous and intramuscular routes of administration. The clinical, macroscopic and histopathological observations demonstrated that a single intramuscular and paravenous administration of Grastofil® was well tolerated and comparable to Neupogen. In addition, Grastofil® and Neupogen showed comparable non-irritant potential.

17. CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG

Cancer Patients Receiving Myelosuppressive Chemotherapy

Filgrastim has been shown to be safe and effective in accelerating the recovery of neutrophil counts following a variety of chemotherapy regimens for a number of cancer types. In a phase 3 clinical trial in small cell lung cancer, patients received subcutaneous administration of filgrastim (4 to 8 µg/kg/day, days 4 to 17) or placebo. In this study, the benefits of filgrastim therapy were shown to be prevention of infection as manifested by febrile neutropenia, decreased hospitalization, and decreased antibiotic usage.

In the phase 3, randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer patients were randomized to receive filgrastim (n = 101) or placebo (n = 110). Of the 211 patients enrolled, 207 patients were evaluable for safety (filgrastim, n = 98; placebo, n = 109) and 199 patients were evaluable for efficacy (filgrastim, n = 95; placebo, n = 104). Filgrastim was started on day 4, after patients received standard dose chemotherapy with cyclophosphamide, doxorubicin and etoposide.

The incidence of febrile neutropenia during cycle 1 was significantly reduced by 51% in the filgrastim group as compared to the placebo group (28% versus 57%, respectively; p < 0.001). The difference in the cumulative incidence of febrile neutropenia over all 6 cycles between the placebo group (77%) and the filgrastim group (40%) was statistically significant (p < 0.001). The incidence of culture confirmed infections was reduced by 50% from 13% to 6.5%.

The absolute neutrophil nadir (severity) and duration of severe neutropenia [days with absolute neutrophil count (ANC) < 0.5 x 10⁹/L] were significantly reduced in all 6 cycles for patients receiving filgrastim compared to placebo (p < 0.005). For all treatment cycles combined, the median duration of severe neutropenia was 6 days per cycle in the placebo group compared to 1 day per cycle in the filgrastim group.

Thus, treatment with filgrastim resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, as well as the severity and duration of severe neutropenia following chemotherapy.

In-patient hospitalization and antibiotic use were evaluated as secondary endpoints (clinical sequelae) to neutropenia. The incidence of febrile neutropenia with hospitalization during cycle 1 was significantly reduced by 50% in the filgrastim group compared to the placebo group (26% versus 55%; $p < 0.001$). Over all 6 cycles there was a 45% reduction in the mean number of days of hospitalization in the filgrastim group compared to the placebo group. Furthermore, there was an overall 47% reduction in the mean number of days of intravenous antibiotic use.

Administration of filgrastim resulted in an earlier ANC nadir following chemotherapy than was experienced by patients receiving placebo (day 10 versus day 12). Filgrastim was well tolerated when given subcutaneously daily at doses of 4 to 8 $\mu\text{g}/\text{kg}$ for up to 14 consecutive days following each cycle of chemotherapy (see **ADVERSE REACTIONS**).

In 36 patients receiving M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for treatment of transitional cell carcinoma of the urothelium, both the severity ($p = 0.0001$) and the duration of granulocytopenia (absolute granulocyte count $< 1.0 \times 10^9/\text{L}$; $p = 0.0001$) were reduced during cycles of chemotherapy in which filgrastim was administered, when compared to cycles of chemotherapy without filgrastim. The accelerated recovery of granulocyte counts during M-VAC cycles when filgrastim was administered resulted in clinically and statistically significant increases in the number of patients eligible to receive planned doses of methotrexate and vinblastine on schedule on cycle day 14 ($p = 0.0001$). Filgrastim was generally well tolerated at all doses treated (up to 115 $\mu\text{g}/\text{kg}/\text{day}$) when administered as a 15 to 30 minute intravenous infusion on days 4 to 11 of the 21-day M-VAC cycle.

In 45 patients treated with melphalan for a variety of advanced malignancies, patients were treated with filgrastim at several doses and using 3 routes of administration (subcutaneous bolus, intravenous, and subcutaneous infusion). This was a dose finding study without controls. A dose-dependent effect on maximum ANC was demonstrated in this study [$p = 0.004$ (non-parametric test of ordered responses)]. Descriptive analysis showed that the period of severe neutropenia (ANC $< 0.5 \times 10^9/\text{L}$) was reduced by filgrastim treatment independent of route.

The effect of filgrastim has also been studied in 12 patients receiving chemotherapy (doxorubicin, ifosfamide with Mesna, and etoposide) for small cell lung cancer. Chemotherapy cycles without filgrastim were alternated with cycles in which filgrastim was administered following chemotherapy. There was a statistically significant reduction in the duration of both severe (ANC $< 0.5 \times 10^9/\text{L}$) and moderate (ANC $< 1.0 \times 10^9/\text{L}$) neutropenia between the filgrastim and no filgrastim groups for cycles 1 and 2 [$p = 0.01$ in each case (Wilcoxon signed-rank test)]. The duration of febrile neutropenia and hospitalization was also reduced. Filgrastim was well tolerated at doses of 1 to 45 $\mu\text{g}/\text{kg}/\text{day}$, given as a continuous infusion on days 4 through 17 of a 21-day chemotherapy cycle.

Sixty-three pediatric patients with advanced neuroblastoma and acute lymphoblastic leukemia (ALL) have received up to 6 cycles of chemotherapy followed with filgrastim. The results indicated that filgrastim is efficacious in reducing the incidence and duration of neutropenia and febrile neutropenia in pediatric patients receiving cytotoxic chemotherapy. These results are comparable to those seen in previous studies involving recombinant stimulating factors as an adjunct to chemotherapy in both adults and children.

Patients with Acute Myeloid Leukemia

In a double-blind, placebo-controlled, multi-center, randomized phase 3 clinical trial, 521 patients (median age 54, range 16-89 yrs.) with de novo acute myeloid leukemia received 1 or 2

courses of induction chemotherapy and then, if in remission, 1 or 2 courses of consolidation chemotherapy.

Treatment with filgrastim significantly reduced the duration of neutropenia and the associated clinical consequences of fever, IV antibiotic use and hospitalization, following induction chemotherapy. In the filgrastim -treated group, the median duration of neutropenia (ANC < 0.5 x 10⁹/L) was reduced by 5 days during the first course of induction therapy (p = 0.0001); fever was reduced by 1.5 days (p = 0.009); the use of IV antibiotics by 3.5 days (p = 0.0001), and the median duration of hospitalization was reduced by 5 days (p = 0.0001). Filgrastim had a similar impact on the duration of neutropenia in subsequent cycles, with reductions in fever, IV antibiotic use and hospitalization. In this trial, the remission rate, time to disease progression and overall survival were similar in both treatment groups.

Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation

In 2 separate randomized, controlled trials, patients with Hodgkin's and non-Hodgkin's lymphoma were treated with myeloablative chemotherapy and autologous bone marrow transplantation (ABMT). In one study (n = 54), filgrastim was administered at doses of 10 or 30 µg/kg/day; a third treatment group in this study received no filgrastim. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 0.5 x 10⁹/L) occurred in the filgrastim -treated group versus the control group [23 days in the control group, 11 days in the 10 µg/kg/day group, and 14 days in the 30 µg/kg/day group, (11 days in the combined treatment groups; p = 0.004)].

In the second study (n = 44; 43 patients evaluable), filgrastim was administered at doses of 10 or 20 µg/kg/day; a third treatment group in this study received no filgrastim. A statistically significant reduction in the median number of days of severe neutropenia occurred in the filgrastim-treated group versus the control group (21.5 days in the control group and 10 days in both treatment groups; p < 0.001). The number of days of febrile neutropenia was also reduced significantly in this study [13.5 days in the control group, 5 days in the 10 µg/kg/day group, and 5.5 days in the 20 µg/kg/day group, (5 days in the combined treatment groups; p < 0.0001)]. Reductions in the number of days of hospitalization and antibiotic use were also seen, although these reductions were not statistically significant. There were no effects on red blood cell or platelet levels.

In a randomized, placebo-controlled trial, 70 patients with myeloid and non-myeloid malignancies were treated with myeloablative therapy and allogeneic bone marrow transplant followed by 300 µg/m²/day of filgrastim. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group; p < 0.001) and time to recovery of ANC to ≥ 0.5 x 10⁹/L (21 days in the control group and 16 days in the treatment group; p < 0.001).

In 3 non-randomized studies (n = 119), patients received ABMT and treatment with filgrastim. One study (n = 45) involved patients with breast cancer and malignant melanoma. A second study (n = 39) involved patients with Hodgkin's disease (HD). The third study (n = 35) involved patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukaemia (ALL), and germ cell tumor. In these studies, the recovery of the ANC to ≥ 0.5 x 10⁹/L ranged from a median of 11.5 to 13 days.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

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

Filgrastim Mobilized PBPC Collection

In 4 studies (n = 126), patients with NHL, HD, ALL, and breast cancer received filgrastim for 6 to 7 days to mobilize haematopoietic progenitor cells into the circulating blood pool where they were collected by 3 aphereses on days 5, 6, and 7 (except for 13 patients in one study who were pheresed on days 4, 6, and 8). In 2 studies, the tested doses and schedules of filgrastim resulted in a greater number of PBPC in the pheresis product compared to the baseline leukapheresis product.

Filgrastim Mobilized PBPC Therapy Followed by Filgrastim

In a randomized study of patients with HD or NHL undergoing myeloablative chemotherapy, 27 patients received filgrastim mobilized PBPC followed by filgrastim and 31 patients received ABMT plus filgrastim. Patients randomized to the filgrastim mobilized PBPC group compared to the ABMT group had significantly fewer median days of platelet transfusions, (6 vs. 10 days; $p < 0.001$), a significantly shorter median time to a sustained platelet count $> 20 \times 10^9/L$, (16 vs. 23 days; $p = 0.02$), a significantly shorter median time to recovery of a sustained ANC $\geq 0.5 \times 10^9/L$ (11 vs. 14 days; $p = 0.005$), and a significantly shorter duration of hospitalization (17 vs. 23 days; $p = 0.002$).

Overall, therapy with filgrastim mobilized peripheral blood progenitor cells provided rapid and sustained haematologic recovery. Long-term (limited to 100 days) follow up haematology data from patients treated with PBPC alone or in combination with bone marrow, was compared to historical data from patients treated with ABMT alone (1 study only). This retrospective analysis indicated that engraftment is durable.

Patients with Severe Chronic Neutropenia

In the phase 3 trial in patients with severe chronic neutropenia (SCN), patients with diagnoses of congenital, cyclic and idiopathic neutropenia were evaluated. Untreated patients had a median ANC of $0.210 \times 10^9/L$. Filgrastim therapy was adjusted to maintain the median ANC between $1.5 \times 10^9/L$ and $10 \times 10^9/L$. A complete response was seen in 88% of patients (defined as a median ANC $1.5 \times 10^9/L$ over 5 months of filgrastim therapy). Overall, complete response to filgrastim was observed in 1 to 2 weeks. The median ANC after 5 months of filgrastim therapy for all patients was $7.46 \times 10^9/L$ (range 0.03 to $30.88 \times 10^9/L$). In general, patients with congenital neutropenia responded to filgrastim therapy with a lower median ANC than patients with idiopathic or cyclic neutropenia.

Dosing requirements were generally higher for patients with congenital neutropenia (2.3 to 40 $\mu g/kg/day$) than for patients with idiopathic (0.6 to 11.5 $\mu g/kg/day$) or cyclic (0.5 to 6 $\mu g/kg/day$) neutropenia.

Overall, daily treatment with filgrastim resulted in clinically and statistically significant reductions in the incidence and duration of fever, infection, and oropharyngeal ulcers. As a result, there also were decreases in requirements for antibiotic use and hospitalization. Additionally, patients

treated with filgrastim reported fewer episodes of diarrhea, nausea, fatigue and sore throat. These clinical findings may translate into improvements in the quality of life in these patients.

Patients with HIV Infection

Filgrastim has been shown to be safe and effective in preventing and treating neutropenia in patients with HIV infection. In a randomized, controlled, multicenter trial of 258 patients, a statistically significant reduction was observed in the incidence of grade 4 neutropenia (ANC < $0.5 \times 10^9/L$, $p < 0.0001$) in filgrastim-treated patients. Three of 172 (1.7%) filgrastim treated patients and 19 of 86 (22.1%) untreated patients experienced confirmed grade 4 neutropenia.

In this randomized study, 85 patients had a total of 128 new or worsening bacterial infections, during the 168 day study period. Of these, a total of 26 events were graded as severe bacterial infections (WHO toxicity grade 3 or higher). The incidence of bacterial infections was decreased by 31% [$p = 0.07$, $p = 0.03$ (adjusted for number of prior opportunistic infections and baseline CD4 count)] and the incidence of severe bacterial infections was decreased by 54% [$p = 0.005$, $p = 0.002$ (adjusted)] in filgrastim-treated patients when compared with untreated patients. In addition, the total number of hospitalizations or prolonged hospitalizations due to a bacterial infection for all groups in this study was 24 events in 21 patients, for a total duration of 392 days. Days of hospitalization for bacterial infection were decreased by 45% [$p = 0.05$, $p = 0.03$ (adjusted)]. A 28% decrease in the number of days of IV antibacterial medications was seen in filgrastim-treated patients [$p = 0.17$, $p = 0.08$ (adjusted)].

In 3 open-label non-randomized clinical studies, the response to filgrastim (ANC > $2 \times 10^9/L$) was observed in a median of 2 - 9 days with either daily or intermittent dosing (see **DOSAGE AND ADMINISTRATION**). Filgrastim therapy was titrated to maintain ANCs between 2×10^9 and $10 \times 10^9/L$.

In the randomized controlled trial, there was a 12% increase in the number of days patients were able to receive full or high-dose myelosuppressive medications. In a multicenter, noncomparative study of 200 patients, filgrastim allowed more than 80% of patients to increase or maintain dosing of ganciclovir, zidovudine, trimethoprim/sulfamethoxazole and pyrimethamine, or to add 1 or more medications to their therapy. The number of these 4 medications received per patient increased by approximately 20% during filgrastim therapy.

In an open-label study to evaluate neutrophil function by *in vitro* chemiluminescence measurement, filgrastim-treated patients had increased oxidase-myeloperoxidase activity and potentially greater microbial killing capacity.

In the randomized controlled study, 13 deaths (5%) were reported on study. There were 13 additional deaths within 30 days of study completion. The leading causes of death were HIV associated complications and AIDS progression. There were no other patterns observed for cause of death. In 3 uncontrolled studies, 16 of the 32 deaths were reported as AIDS progression, the other 16 deaths were attributed to HIV-associated complications. In these clinical studies, all deaths were reported by the investigator as not related or unlikely to be related to filgrastim.

In clinical trials, changes in HIV viral load were evaluated by a quantitative HIV-1 RNA RT-Polymerase Chain Reaction (PCR) analyses and by measurement of HIV-1 p24 antigen levels. These studies did not show any evidence of increased HIV replication associated with filgrastim administration.

18. NON-CLINICAL TOXICOLOGY – REFERENCE BIOLOGIC DRUG

Recombinant human granulocyte colony stimulating factor (r-metHuG-CSF) was administered to monkeys, dogs, hamsters, rats and mice as part of a comprehensive pre-clinical toxicology program which included both single-dose acute, repeated dose subacute and chronic studies.

Single-dose administration of r-metHuG-CSF by the oral, intravenous, subcutaneous, or intraperitoneal route resulted in no significant toxicity in mice, rats or hamsters at doses up to 115 µg/kg/animal (862.5 µg/kg based on group mean pre-study body weights). The increased leukocyte counts observed in monkeys on day 7 was an expected result of the pharmacological activity of r-metHuG-CSF and this had returned to control values by day 14. Consequently, the single-dose LD50 of r-metHuG-CSF in these species is in excess of 3,450 µg/kg, which is at least 50- to 600-fold greater than the highest anticipated human clinical dose.

In the subacute, repeated-dose studies, the changes observed with r-metHuG-CSF can be attributed to the anticipated pharmacological actions of the protein. In rats, hamsters, dogs and monkeys, increased granulopoiesis was evidenced by dose-dependent increases in total white blood cell counts, an increased proportion of segmented neutrophils in the circulation, and an increase in the myeloid to erythroid ratio in the bone marrow. In the 14-day monkey study and 13-week rat study, platelet counts were reduced in the 2 high dose groups. In all species, histopathologic examinations of the liver and spleen revealed evidence of ongoing extramedullary granulopoiesis. Increased spleen weights were seen in all species and appeared to be dose-related.

Few significant changes in blood biochemistry values were observed in rats, hamsters, dogs, or monkeys. However, a dose-dependent increase in serum alkaline phosphatase was observed in rats. This increase may be reflective of increased activity of osteoblasts and osteoclasts, as published evidence indicates that osteoclasts are derived from haematopoietic precursors. The stimulatory effect of r-metHuG-CSF on granulopoiesis may, therefore, produce an imbalance in the normal equilibrium between osteoclasts and osteoblasts. The finding of increased osteoclasts and osteoanagenesis in the hind legs (which account for 30% of haematopoiesis in rats) is consistent with this hypothesis. Changes noted in serum chemistry values were readily reversible upon discontinuation of treatment and do not appear to be of serious toxicological consequence.

Whereas rats survived 13 weeks of daily administration of r-metHuG-CSF at dose levels up to 575 µg/kg, 5 of 8 (4 males and 1 female) monkeys given r-metHuG-CSF at 1,150 µg/kg died within 18 days. Death was preceded by signs of neurological toxicity and was associated with 15- to 28-fold increases in peripheral leukocyte counts and neutrophil-infiltrated haemorrhagic foci in both the cerebrum and cerebellum. In contrast, no monkeys died following 13 weeks of daily intravenous administration of r-metHuG-CSF at a dose level of 115 µg/kg.

No hamsters or dogs died following 14 days of intravenous r-metHuG-CSF administration at doses up to 34.5 µg/animal (equivalent to 213.9 µg/kg based on group mean pre-study body weights) and 345 µg/kg, respectively. One monkey in the control group died in the 14-day study. Consequently, the lethal dose of r-metHuG-CSF is greater than 115 µg/kg/day and death was associated with a gross exaggeration of granulopoietic activity.

19. SUPPORTING PRODUCT MONOGRAPHS

Neupogen (sterile solution for injection, 300 µg/mL and 600 µg/mL), Submission Control Number 202310, Product Monograph, Amgen Canada Inc., (Apr, 19, 2017).

Neupogen is a trademark of Amgen Inc.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Grastofil® (pronounced) GRAS-toh-fill **filgrastim Injection**

Read this carefully before you start taking **Grastofil®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Grastofil®**.

Grastofil® is a biosimilar biologic drug (biosimilar) to the reference biologic drug Neupogen. A biosimilar is authorized based on similarity to a reference biologic drug that was already authorized for sale.

Serious Warnings and Precautions

- Your spleen may become enlarged and rupture while taking **Grastofil®**. A ruptured spleen can cause death. Call your doctor right away if you or your child has pain in the left upper stomach area, or left shoulder tip area.
- If you have sickle cell trait or sickle cell disease, make sure that you tell your doctor before you start taking **Grastofil®** so that the potential risks and benefits can be discussed. In patients with sickle cell trait or sickle cell disease, severe sickle cell crises have been associated with the use of **Grastofil®**, resulting in death in some cases.

What is **Grastofil® used for?**

Grastofil® is used to treat neutropenia (nu-tro-**peen**-ee-ah), a condition where the body makes too few neutrophils. Neutropenia may be a long-standing condition where your body does not make enough neutrophils, or it may be caused by drugs used to treat cancer. In some cases, your body may make enough neutrophils, but as a part of your treatment for cancer, your doctor may want to increase the number of certain blood cells (CD34 cells) and collect them. The cells are collected using a process called apheresis (ay-fer-**ree**-sis). These collected cells are given back to you after you receive very high doses of treatment for cancer to make your blood counts get back to normal more quickly.

How does **Grastofil® work?**

Grastofil® is a man-made form of granulocyte colony stimulating factor (G-CSF), which is made using the bacteria *E coli*. G-CSF is a substance naturally produced by the body. It stimulates the growth of neutrophils (**nu**-tro-fils), a type of white blood cell important in the body's fight against infection. **Grastofil®** works by helping the body make more neutrophils. To make sure **Grastofil®** is working, your doctor will ask that you have regular blood tests to count the number of neutrophils you have. It is important that you follow your doctor's instructions about getting these tests.

What are the ingredients in **Grastofil®?**

Medicinal ingredients: filgrastim

Non-medicinal ingredients: acetate, polysorbate 80, sodium, sorbitol (E420), and water for injection

The pre-filled syringe components contain natural rubber (a derivative of latex), which should not be handled by persons sensitive to this substance.

Grastofil® comes in the following dosage forms:

Grastofil® is available in single-use graduated (1/40 graduations from 0.1 mL to 1.0 mL) pre-filled syringes with an UltraSafe Passive® Needle Guard, as a clear, colourless injection in two sizes of 300 mcg/0.5mL and 480 mcg/0.8 mL (both containing 600 mcg/mL of filgrastim). These are available in cartons of 1 and 10 individually blistered pre-filled syringes per carton.

Do not use Grastofil® if:

- You are allergic (hypersensitive) to filgrastim or any of its ingredients. For a detailed list of medicinal and nonmedicinal ingredients, see above “**What are the ingredients in Grastofil®?**”.
- You are allergic to other medicines made using the bacteria *E.coli*. Ask your doctor if you are not sure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Grastofil®. Talk about any health conditions or problems you may have, including if you:

- Get left upper abdominal pain or pain at the tip of your shoulder,
- Have osteoporosis (loss of calcium from the bones which leads to the bones becoming weak and fragile),
- Are suffering from any other illness (especially if you think you may have an infection),
- Experience a cough, fever and difficulty breathing,
- Have sickle cell trait or sickle cell disease (an inherited blood disorder that affects red blood cells),
- Get left upper abdominal pain or pain at the tip of your shoulder,
- Are taking or have recently taken any other medicines, including medicines obtained without a prescription,
- Are breast-feeding,
- Are pregnant, or think you may be pregnant or plan to get pregnant.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**The following may interact with Grastofil®:**

Interactions between Grastofil® and other drugs have not been studied. Drugs such as lithium may affect the release of neutrophils into your blood stream. You should discuss your treatment with your doctor before using Grastofil®.

How to take Grastofil®:

If you/your child are receiving Grastofil® because you are also receiving chemotherapy, the last dose of Grastofil® should be injected at least 24 hours before your next dose of chemotherapy.

Usual dose:

Your doctor will determine your/your child's correct dose based on your/your child's body weight.

Overdose:

You must always use the correct dose of Grastofil®. Too little Grastofil® may not protect you against infections, and too much Grastofil® may cause too many neutrophils to be in your blood.

If you think you have taken too much Grastofil®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Grastofil® should be injected at the same time each day. If you miss a dose contact your doctor or nurse.

Information on How to Inject Grastofil®:

This section contains information on how to give an injection of Grastofil®. **It is important that you do not try to give the injection unless you have received training from your doctor or nurse.** If you are not sure about giving the injection or you have any questions, please ask your doctor or nurse for help.

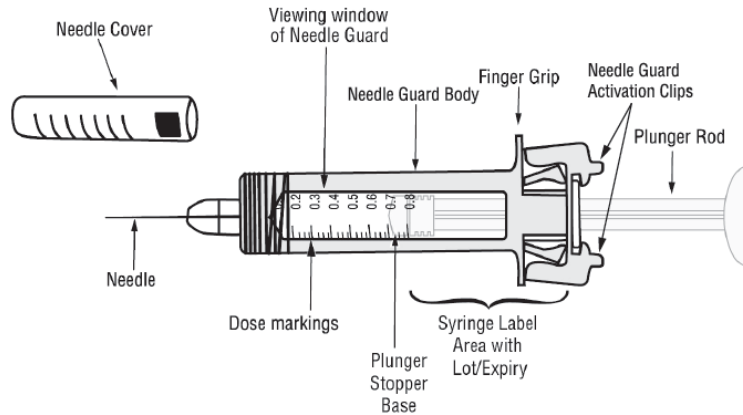
Injecting with Grastofil®:

You will need to give an injection into the tissue under the skin, known as a subcutaneous injection. Your doctor or nurse will tell you how frequently it should be injected.

Before Injecting Grastofil®:

To give a subcutaneous injection you will need:

1. A new pre-filled syringe of Grastofil® with an UltraSafe Passive® Needle Guard.



2. Alcohol wipes or similar.
3. Cotton or gauze.
4. A puncture-proof container for disposing of used syringes, as discussed with your doctor/nurse.

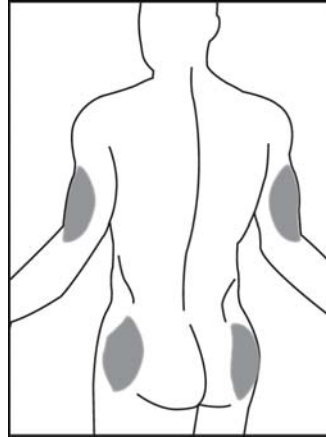
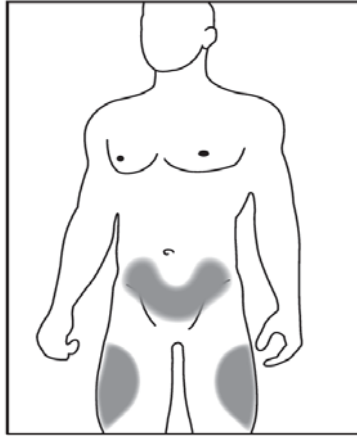
Setting-up for the Injection:

1. Remove one Grastofil® pre-filled syringe in the blister packaging from the refrigerator and leave it unopened on your working surface for about 30 minutes so that it reaches room temperature. Confirm on the syringe and carton that it is the correct dose (300 mcg/0.5 mL or 480 mcg/0.8 mL Grastofil®) as prescribed by your doctor.
2. Check the expiry date which is stated on the carton and syringe label (see EXP). Do not use it if the date has passed the last day of the month shown.
3. Do not shake the pre-filled syringe as vigorous shaking may damage the medication. Check the appearance of Grastofil®. It must be clear. If it is cloudy or there are particles in it, you must not use it.
4. Clean your hands thoroughly with soap and water and/or hand sanitizer.
5. Find a comfortable, well-lit place and put the syringe, the alcohol wipes, cotton or gauze, and the puncture-proof container where you can reach them.
6. Keep the needle cover on the needle until you are ready to inject or measure your dose and inject.

Choosing an Injection Site:

The most suitable injection sites (places on your body) to inject Grastofil® are:

- The outer area of your upper arms
- The front of your middle thighs
- The abdomen, **except for the 2 inches area around the navel**
- Upper outer area of your buttocks



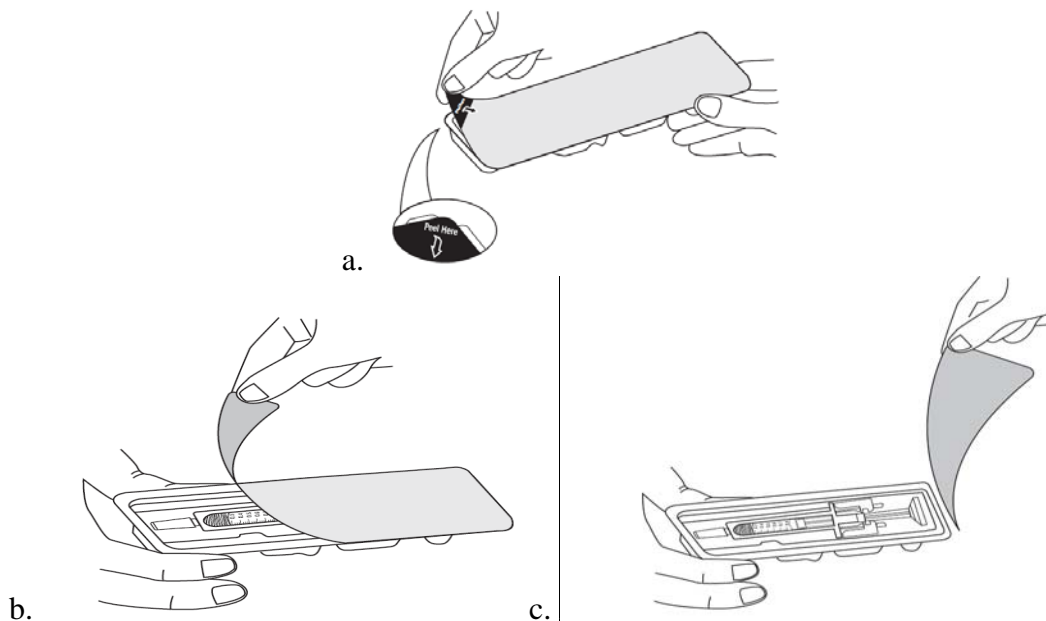
From the above options, change the injection site each time you take an injection so that you do not develop soreness in one area. Do not inject into the same site that is tender, red, bruised or hard or that has scars or stretch marks.

How do I give my injection?

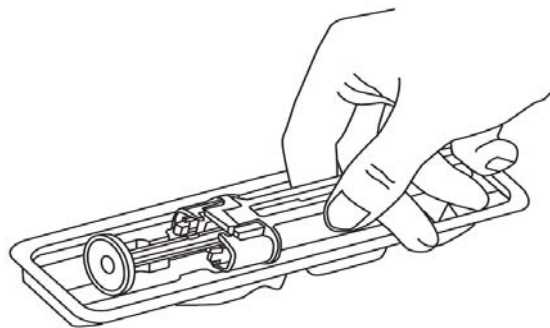
IMPORTANT: REMOVAL OF INDIVIDUAL SYRINGE FROM BLISTER PACKAGING

Follow directions for correct handling technique as shown below when removing the pre-filled syringe with the UltraSafe Passive[®] Needle Guard from the packaging, otherwise, the needle's safety mechanism may be triggered, making the syringe unusable.

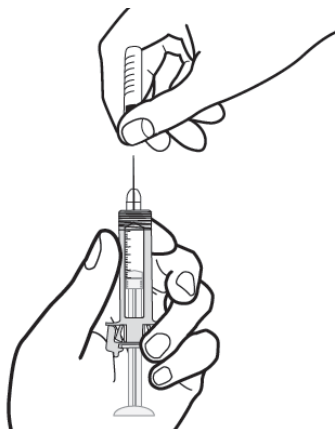
1. Starting in the corner as indicated by the arrow and "Peel Here" on the top layer, open the blister pack by peeling back the top layer **COMPLETELY OFF**.



2. Remove the syringe from the blister pack **by the body** as shown below. **Do not** lift the product by the plunger or needle cover. **Do not** touch the needle guard activation clips at any time during use. This may trigger the needle's safety mechanism causing the needle to retract (pull back) before your injection is given. This will make the syringe unusable.



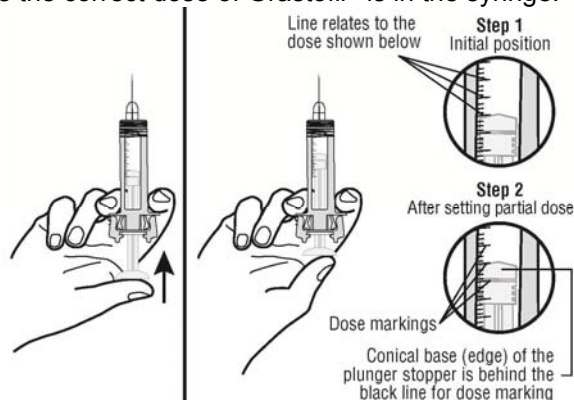
3. You must **always clean** the skin on the selected injection site by using an alcohol wipe.
4. Hold the pre-filled syringe by the body (needle guard) with the needle pointing up and avoid touching the needle guard activation clips. Holding the syringe by the body with the needle pointing up helps to prevent the medicine from leaking out of the needle. **Carefully pull the needle cover straight off without twisting it. Do not touch the needle or plunger. Do not use if the syringe is damaged or needle is bent.** If the syringe is damaged or needle is bent, throw away (dispose of) the syringe in the puncture-proof container.



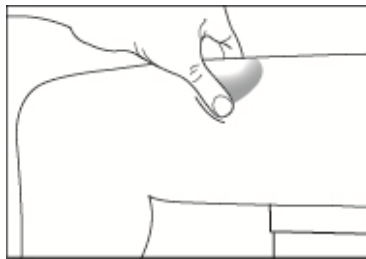
For patients injecting the full content of your syringe (as prescribed by your doctor), proceed to Step 5.

For patients injecting a partial dose only (as prescribed by your doctor): Holding the pre-filled syringe as shown in the image below, press slowly on the plunger to push out the excess medicine until the conical base of the plunger stopper lines up with the syringe marking for your prescribed dose.

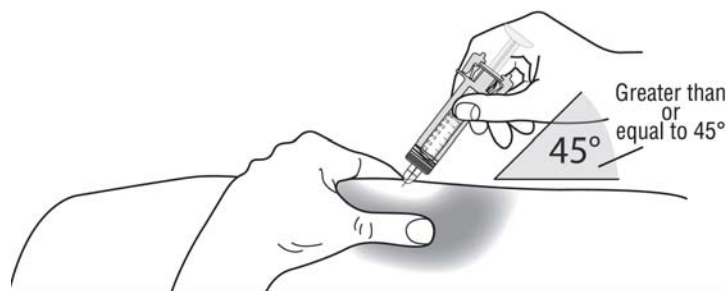
Check again to make sure the correct dose of Grastofil[®] is in the syringe.



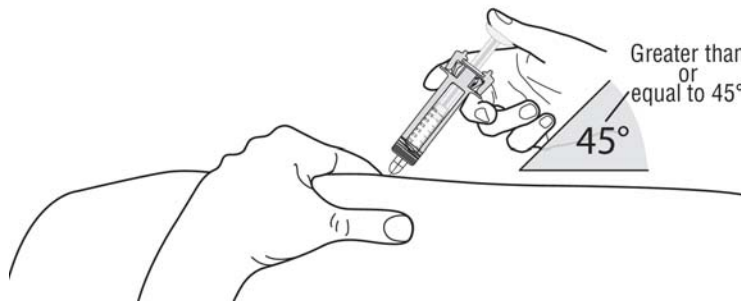
5. Hold the pre-filled syringe between the thumb and forefinger of the hand you will use to inject Grastofil[®]. Use the other hand to pinch a fold of the skin at the cleaned injection site between your thumb and forefinger, without squeezing it as shown below.



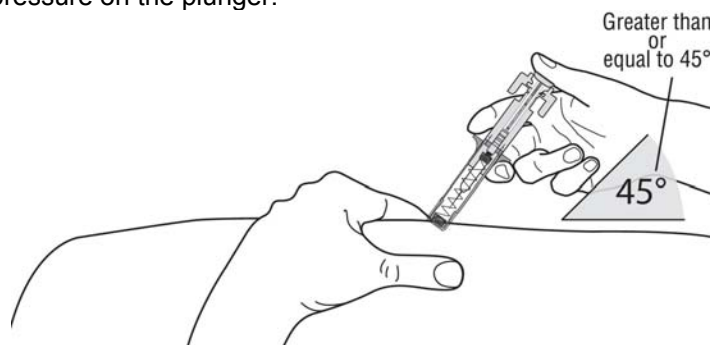
6. Insert the needle under the skin at an angle of approximately greater than or equal to 45° as shown by your doctor or nurse.



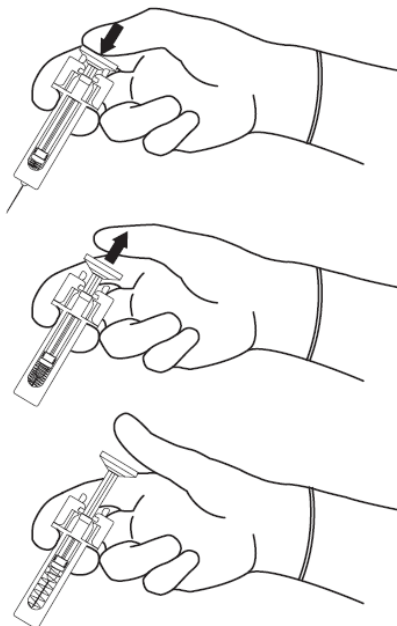
7. After the needle is inserted, let go of the fold of the skin. Inject the prescribed dose by pushing the plunger with your thumb while grasping the finger grips as shown in the image below and as directed by your doctor or nurse.



8. Press the plunger slowly and completely, until all of the medication has been injected as shown below. The needle guard will not be activated unless the entire dose has been administered and you remove downward pressure on the plunger.



When the syringe is emptied of all the medication, slowly lift your thumb from the plunger which will release the needle-guard. The needle will then withdraw from the skin and be covered and locked in place by the needle-guard.



9. After the injection, immediately place cotton or gauze on the injection site and apply pressure for several seconds. Do not use Grastofil[®] that is left in the syringe.
10. Place the pre-filled syringe with the needle guard covered needle into a puncture-proof container for proper disposal as described below. Use each pre-filled syringe only for one injection.

Remember:

Do not hesitate to consult your doctor or nurse for help or if you have any concerns.

Disposal of Used Syringes:

The used syringes should be disposed of in accordance with local requirements.

- Put used syringes into an appropriate puncture-proof container as instructed by your doctor/nurse.
- **Always** keep this container **out of reach and sight of children**.
- When the puncture-proof container is full, it should be disposed as instructed by your doctor, nurse or pharmacist. **Do not throw the container in the household trash. Do not recycle.**
- Never put used syringes into your normal household waste bin.

What are possible side effects from using Grastofil[®]?

These are not all the possible side effects you may feel when taking Grastofil[®]. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions. Like all medications, Grastofil[®] may show side effects upon use and based on individual response.

Spleen Rupture: Your spleen may become enlarged and can rupture while taking Grastofil[®]. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you or your child has pain in the left upper stomach area or left shoulder tip area. This pain could mean you or your child's spleen is enlarged or ruptured.

Serious Allergic Reactions: Grastofil® can cause serious allergic reactions. These reactions can cause body rash, shortness of breath, wheezing, dizziness, swelling, fast pulse, and sweating. If you or your child starts to have any of these symptoms, stop using Grastofil® and call your doctor or seek emergency care right away. If you or your child has an allergic reaction during the injection of Grastofil®, stop the injection right away

A serious lung problem called acute respiratory distress syndrome (ARDS): Call your doctor or seek emergency care right away if you or your child has shortness of breath, trouble breathing or a fast rate of breathing.

Sickle Cell Crisis: Call your doctor or seek emergency care right away if you or your child experiences severe pain in the bones, chest, gut or joints.

Kidney injury (glomerulonephritis): Call your doctor right away if you experience puffiness in your face or ankles, blood in your urine or brown coloured urine, or if you notice that you urinate less often than usual.

The common side effects of use of Grastofil® are: The most common side effect you/your child may experience is bone, joint and muscle pain. This pain can be relieved by taking a non-acetylsalicylic acid pain reliever such as acetaminophen.

In addition, other common side effects can be fatigue, headache, loss of appetite, diarrhea, cough, sore throat, elevation in liver enzymes, reduction in platelets (cells involved in clotting), which increases the risk of bleeding or bruising.

Some people may experience a lump, redness, swelling, bruising or itching at the site of injection. This may be an allergy to the ingredients or could be a local reaction. **If at any time a serious allergic reaction occurs, immediately call the doctor or emergency services (for example, call 911).**

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.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON: ≥ 10% Bone pain		√	
COMMON: ≥ 1% and < 10% Splenomegaly (including the following symptoms: pain in the left upper stomach area or left shoulder tip area)		√	
Osteoporosis in children with severe chronic neutropenia (including decreased bone density, making them weak, more brittle and likely to break)		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON: $\geq 0.1\%$ and $< 1\%$ Splenic rupture (including the following symptoms: left upper abdominal pain or pain at the tip of your shoulder) Capillary Leak Syndrome (including the following symptoms: swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness)		√	√
		√	√
RARE: ≥ 0.01 and $< 0.1\%$ Allergic reactions [body rash, shortness of breath, a drop in blood pressure (usually causing dizziness or light headedness), swelling around the mouth or eyes, fast pulse, weakness, sweating, severe redness or swelling or itching at injection site] Acute respiratory distress syndrome (including the symptoms: fever, shortness of breath, cough, or congestion in your lungs) Cutaneous Vasculitis (including the following signs: inflammation of the blood vessels in the skin) Sweet's Syndrome (including the following symptoms: plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever)		√	√
		√	√
		√	√
		√	√
VERY RARE: $< 0.01\%$ Alveolar hemorrhage and hemoptysis (including the following symptoms: bleeding from the lungs and coughing of blood) Pseudogout (including the following symptoms in patients treated for cancer: pain and swelling of the joints, similar to gout)		√	√
		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on [Adverse Reaction Reporting](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax, or;
- Calling 1-866-234-2345;

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use Grastofil[®] after the expiry date which is stated on the outer carton and on the pre-filled syringe.

- Store in a refrigerator (2°C - 8°C). Do not freeze. Do not shake.
- If Grastofil[®] is accidentally frozen, allow it to thaw in the refrigerator before giving the next dose. However if it is frozen for a second time, do not use it and contact your doctor or nurse for further instructions.
- Grastofil[®] can be removed from the refrigerator and left at room temperature (not above 25°C) for a single period of up to 15 days that ends within the labelled expiry date. Once Grastofil[®] has been out at room temperature it should not be put back into the refrigerator. Any Grastofil[®] syringes that have been out of the refrigerator for longer than 15 days should not be used and should be disposed of in accordance with local requirements.
- Keep the pre-filled syringe in the carton in order to protect from light. Do not use if you notice it is cloudy or there are particles in it.

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

Keep out of reach and sight of children.

If you want more information about Grastofil[®]:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](http://hc-sc.gc.ca/index-eng.php) (<http://hc-sc.gc.ca/index-eng.php>); Apotex's website at <http://www.apotex.ca/products>, or by contacting DISpedia, Apotex's Drug Information Service at: 1-800-667-4708

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

UltraSafe Passive[®] is a trademark of Safety Syringes, Inc., parent company is Becton, Dickinson and Company.

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