PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}NIVESTYM™

Filgrastim injection

Sterile Solution

300 mcg/0.5 mL and 480 mcg/0.8 mL in a single-use prefilled syringe
300 mcg/1 mL and 480 mcg/1.6 mL in a single-use vial

(Subcutaneous or Intravenous Use Only)

Hematopoietic Agent

Granulocyte Colony-Stimulating Factor

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Nivestym (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 Nivestym and the reference biologic drug Neupogen.

Nivestym (filgrastim injection) is indicated for:

- **Cancer Patients Receiving Myelosuppressive Chemotherapy**

Nivestym (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.

Nivestym 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 Nivestym therapy to avoid leukocytosis and to monitor the neutrophil count. In phase 3 clinical studies, filgrastim therapy was discontinued when the absolute neutrophil count (ANC) was > 10 x 10^9/L after expected chemotherapy-induced nadir.

- **Patients with Acute Myeloid Leukemia**

Nivestym 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**

Nivestym is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, 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**

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

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

Nivestym 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**

Nivestym is indicated in patients with HIV infection for the prevention and treatment of neutropenia, to maintain a normal ANC (eg, between 2 x 10^9 and 10 x 10^9/L). Nivestym 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 (eg, initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter, or as clinically indicated) during Nivestym therapy (see **Monitoring and Laboratory Tests**).

2 CONTRAINDICATIONS

Nivestym (filgrastim) is contraindicated in patients with known hypersensitivity to *E. coli* derived products, filgrastim, pegfilgrastim, or to any ingredient in the formulation, including any non-medicinal ingredient. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Splenic rupture, including fatal cases, has 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

4.1 Dosing Considerations

- **General Considerations**

Nivestym in a graduated prefilled syringe with a BD UltraSafe Plus™ Passive Needle Guard may not accurately measure volumes less than 0.3 mL (180 mcg). Therefore, patients weighing less than 36 kg cannot be accurately dosed at a dose of 5 mcg/kg/day.

- **Cancer Patients Receiving Myelosuppressive Chemotherapy**

Nivestym should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Nivestym 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**

Nivestym 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 Nivestym (filgrastim) in adult patients is 5 mcg/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 mcg/kg/day administered subcutaneously. Note that patients weighing less than 36 kg cannot be accurately dosed with the prefilled syringe at this dose or lower (see **4.1 Dosing Considerations**).

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

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

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

The recommended dose of Nivestym following bone marrow transplant is 10 mcg/kg/day given as an intravenous infusion of 4 or 24 hours, or as a continuous 24-hour subcutaneous infusion.

During the period of neutrophil recovery, the daily dose of Nivestym should be titrated against the neutrophil response as follows:

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

*If ANC decreases to < 1.0 x 10^9/L at any time during the 5 mcg/kg/day administration, Nivestym should be increased to 10 mcg/kg/day, and the above steps should then be followed.

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

The recommended dose of Nivestym for PBPC mobilization is 10 mcg/kg/day given as a single daily subcutaneous injection or a continuous 24-hour infusion. Nivestym 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 hematopoietic progenitor cells is obtained. For peripheral blood progenitor cells mobilized with Nivestym, 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 reinfused 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 hematopoietic 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 number of progenitor cells, measured as CD34+ or GM-CFU, are not standardized and variations may exist between laboratories, and
- Factors other than Nivestym 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 Nivestym following PBPC transplant is 5 mcg/kg/day given either subcutaneously or as an intravenous infusion. The daily dose of Nivestym 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 Nivestym is 1 mcg/kg/day or 300 mcg 3 times per week by subcutaneous injection until a normal neutrophil count is reached and can be maintained (ANC ≥ 2 x 10^9/L). Dose adjustments may be necessary as determined by the patient's ANC to maintain the ANC between 2 x 10^9 and 10 x 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 mcg 3 times per week by subcutaneous injection is recommended. A further dose adjustment may be necessary to maintain the ANC between 2 x 10^9 and 10 x 10^9/L.

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

- **Patients with Severe Chronic Neutropenia**

Starting Dose

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

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

Dose Adjustments

Nivestym may be administered subcutaneously as a single daily injection to increase and sustain the ANC above 1.5 x 10^9/L. Chronic daily administration is required to maintain an adequate neutrophil count. After 1 to 2 weeks of therapy, the initial dose may be doubled or

halved. Subsequently, the dose may be individually adjusted not more than every 1 to 2 weeks to maintain the ANC between 1.5 x 10^9/L and 10 x 10^9/L. WBC/ANC monitoring should be done more frequently (eg, every other day) if the ANC reaches values above 25 x 10^9/L, and the dose reduced if the ANC remains greater than 25 x 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 mcg/kg; Cyclic Neutropenia 2.1 mcg/kg; Idiopathic Neutropenia 1.2 mcg/kg.

In clinical trials in patients with SCN, 91% of patients who responded to filgrastim therapy responded at doses of ≤ 12 mcg/kg/day. Ninety-seven percent of patients responded at doses of ≤ 24 mcg/kg/day. Therefore, patients with SCN who do not respond to the recommended starting dose should be treated with up to 24 mcg/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

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

Nivestym should not be vigorously shaken.

Nivestym is supplied in either vials or in graduated prefilled syringes with BD UltraSafe Plus™ Passive Needle Guard. Following administration of Nivestym from the prefilled syringe, the Needle Guard is automatically activated to cover the needle after the injection is given. The Needle Guard will help prevent stick injuries to anyone who handles the prefilled syringe. The prefilled syringe should be disposed of by placing the entire prefilled syringe with activated Needle Guard into an approved puncture-proof container.

In those situations in which the physician determines that the patient can safely and effectively self-administer Nivestym, 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-resistant 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, Nivestym may be diluted in 5% dextrose. Nivestym diluted to a concentration between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) at a concentration of 2.0 mg/mL. When diluted in 5% dextrose or 5% dextrose plus Albumin (Human), Nivestym is compatible with glass bottles, PVC and polyolefin intravenous bags and polypropylene syringes.

Dilution of Nivestym to a final concentration of < 5 mcg/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 Missed Dose

Nivestym should be injected at the same time each day. Patients who miss a dose should be 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 ≥ 69 mcg/kg/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 x 10^9/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 x 10^9/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 pre-treatment 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 and Strengths

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Subcutaneous (SC) or Intravenous (IV)	Sterile Solution for injection: Prefilled syringes (600 mcg/mL) • 300 mcg/0.5 mL in a single-use graduated prefilled syringe with a BD Ultrasafe Plus™ Passive Needle Guard • 480 mcg/0.8 mL in a single-use graduated prefilled syringe with a BD Ultrasafe Plus™ Passive Needle Guard Vials (300 mcg/mL) • 300 mcg/1mL in a single-use vial • 480 mcg/1.6 mL in a single-use vial	Acetate, polysorbate 80, sodium, sorbitol, and water

Composition

Nivestym (filgrastim) is a sterile, clear, colorless, preservative-free liquid for parenteral administration. The product is available in 1 mL single-use graduated prefilled syringes and 2 mL single-use vials. The single-use prefilled syringes are available in two strengths; 300 mcg/0.5 mL and 480 mcg/0.8 mL. The single-use vials are available in two strengths; 300 mcg/1 mL and 480 mcg/1.6 mL.

See **Table 2** for product composition of each prefilled syringe and single-use vial.

Table 2: Nivestym Product Composition for Single-use Prefilled Syringe and Vial

	300 mcg/0.5 mL Prefilled syringe	**480 mcg/0.8 mL Prefilled syringe**	**300 mcg/1 mL Vial**	**480 mcg/1.6 mL Vial**
Filgrastim	300 mcg	480 mcg	300 mcg	480 mcg
Acetate	0.295 mg	0.472 mg	0.59 mg	0.94 mg
Polysorbate 80	0.02 mg	0.032 mg	0.04 mg	0.064 mg
Sodium	0.0175 mg	0.028 mg	0.035 mg	0.056 mg
Sorbitol	25 mg	40 mg	50 mg	80 mg
Water for injection q.s. ad*	0.5 mL	0.8 mL	1 mL	1.6 mL
*quantity sufficient to make				

Packaging

Prefilled Syringes

Single-use, preservative-free, graduated prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard, containing 300 mcg/0.5 mL of filgrastim.

- Pack of 1 prefilled syringe
- Pack of 10 prefilled syringes

Single-use, preservative-free, graduated prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard, containing 480 mcg/0.8 mL of filgrastim.

- Pack of 1 prefilled syringe
- Pack of 10 prefilled syringes

Nivestym: Use only 1 dose per prefilled syringe. Discard unused portions. Do not save unused drug for later administration.

The syringe plunger stopper and needle cover are not made with natural rubber latex.

Vials

Single-use, preservative-free vials containing 300 mcg/1 mL of filgrastim. Dispensing packs of 10 vials.

Single-use, preservative-free vials containing 480 mcg/1.6 mLof filgrastim. Dispensing packs of 10 vials.

Nivestym: Use only 1 dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

The vial stopper is not made with natural rubber latex.

7 DESCRIPTION

Nivestym (filgrastim) 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 in *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 rupture, including fatal cases, has been reported following the administration of filgrastim. Patients receiving Nivestym (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 filgrastim 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 Nivestym in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy (see **DOSAGE AND ADMINISTRATION**).

The efficacy of filgrastim has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas) or with mitomycin C or with myelosuppressive doses of anti-metabolites such as 5-FU or cytosine arabinoside.

The safety and efficacy of filgrastim have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of Nivestym with chemotherapy and radiation therapy should be avoided.

Carcinogenesis and Mutagenesis
The carcinogenic potential of filgrastim 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 mcg/kg.

Growth Factor Potential
Filgrastim is a growth factor that primarily stimulates production of neutrophils. However, the possibility that filgrastim 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 leukemia (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 Nivestym 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 Nivestym should be monitored closely.

Aortitis

Aortitis has been reported in patients receiving filgrastim and may present with generalized signs and symptoms such as fever and increased inflammatory markers. Consider aortitis in patients who develop these signs and symptoms without known etiology.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) has been reported after the administration of filgrastim or pegfilgrastim. CLS can cause circulatory shock and may be fatal, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity, and may be 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.

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 Nivestym for such patients, and only after careful consideration of the potential risks and benefits.

The response to Nivestym 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-hematological 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 x 10^9/L or greater were observed in approximately 2% of patients receiving filgrastim at doses above 5 and up to

115 mcg/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 Nivestym therapy (see **Monitoring and Laboratory Tests**).

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy
During the period of administration of Nivestym for PBPC mobilization in cancer patients, discontinuation of Nivestym is appropriate if the leukocyte count rises to > 100 x 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 reactions and anaphylactic reactions occurring on initial or subsequent treatment has been reported in < 1 in 4,000 patients treated with filgrastim. These reactions have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, 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 Nivestym 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 Nivestym 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 filgrastim 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 and 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 crossreact with endogenous G-CSF, resulting in immune-mediated neutropenia; however, this has not been reported in clinical studies or in post-marketing experience with filgrastim. 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 Nivestym therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when filgrastim was administered, and 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 Myeloablative Chemotherapy Followed by Bone Marrow Transplantation
A CBC and platelet count should be obtained at regular intervals (3 times per week during Nivestym therapy) following marrow infusion.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy
After 4 days of Nivestym 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 Nivestym 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 (ie, 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 Nivestym 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 Nivestym therapy and at regular intervals (eg, initially twice weekly for 2 weeks, once weekly for an additional 2 weeks, then once monthly thereafter, or as clinically indicated) during Nivestym therapy. Some patients may respond very rapidly and with a considerable increase in neutrophil count to the initial doses of Nivestym. It is recommended that blood samples be drawn for ANC measurement prior to any scheduled dosing with Nivestym.

Renal

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.

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 Nivestym who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Nivestym should be 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 PBPC mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of Nivestym 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 to 2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, Nivestym therapy should be continued following chemotherapy until the post nadir ANC reaches 10 x 10^9/L. Therefore, the premature discontinuation of Nivestym 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 Nivestym 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 Nivestym therapy. The safety and efficacy of Nivestym in the treatment of neutropenia or pancytopenia due to other hematopoietic disorders (eg, 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 Nivestym 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 Nivestym administration in patients with abnormal cytogenetics is unknown. If a patient with SCN develops abnormal cytogenetics, the risks and benefits of continuing Nivestym 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 pediatric patients with SCN in the post-market setting. Patients with SCN, particularly those 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 Nivestym therapy. Other infrequently observed adverse events included exacerbation of some pre-existing skin disorders (eg, psoriasis), cutaneous vasculitis (leukocytoclastic), alopecia, hematuria/proteinuria, thrombocytopenia (platelets < 50 x 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 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 Nivestym 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 embryolethality were observed in animals treated with filgrastim at 80 mcg/kg/day. Filgrastim administered to pregnant rabbits at doses of 80 mcg/kg/day during the period of organogenesis was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities, decreased body weight, live births, and food consumption. External abnormalities were not observed in the fetuses of dams treated at 80 mcg/kg/day. Reproductive studies in pregnant rats have shown that filgrastim was not associated with lethal, teratogenic, or behavioral effects on fetuses when administered by daily intravenous injection during the period of organogenesis at dose levels up to 575 mcg/kg/day.

In Segment III studies in rats, offspring of dams treated at greater than 20 mcg/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 mcg/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. Nivestym should be used during pregnancy only if the potential benefit justifies any potential theoretical risk to the fetus.

8.1.2 Breast-feeding

It is not known whether filgrastim is excreted in human milk, therefore, Nivestym is not recommended for use in nursing women.

8.1.3 Pediatrics

Neonates
The safety and efficacy of filgrastim in neonates have not been established.

Pediatrics (< 18 years of age)

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 Nivestym 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 **General (Splenic Rupture)**,

Respiratory (ARDS), **Hypersensitivity/Allergic Reactions** and **Hematologic** (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 mcg/kg/day) administered intravenously, and less frequently in patients treated with lower subcutaneous doses of filgrastim (3 to 10 mcg/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 mcg/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 3: Percentage of Blinded Cycles with Events

	% 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
Mucositis	12	20
Fever	12	11
Fatigue	11	16

	% of Blinded Cycles with Events	
Event	**Filgrastim Patient Cycles N = 384**	**Placebo Patient Cycles n = 257**
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, 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 as 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, 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 as 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 x 10^9/L with WBC count increases during the mobilization period ranging from 16.7 x 10^9/L to 138 x 10^9/L above baseline. Eighty-eight percent of patients had an increase in WBC count between 10 x 10^9/L and 70 x 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 x 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 x 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 x 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 hemorrhagic 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 possibly 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 acute respiratory distress syndrome 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, 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 clinical 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

Adverse reactions listed under specific indications can also be seen across 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 ≥ 5% higher incidence in filgrastim treated patients compared to controls: paresthesia, erythema, 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 the results of studies in pediatric patients with the reference biologic drug labelling.

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: Hematologic (Leukocytosis)**)
- Bone Pain
- Glomerulonephritis (see **WARNINGS AND PRECAUTIONS: Renal (Glomerulonephritis)**)
- Aortitis (see **WARNINGS AND PRECAUTIONS: Cardiovascular (Aortitis)**)

10 DRUG INTERACTIONS

10.1 Overview

Interactions of filgrastim with other cytokines, including hematopoietic 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.

10.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

10.3 Drug-Food Interactions

Interactions with food have not been established.

10.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.5 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 hematopoietic cell types. 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 mcg/kg/day. This increase in neutrophil counts was observed whether filgrastim was administered intravenously (1 to 70 mcg/kg twice daily), subcutaneously (1 to 3 mcg/kg once daily), or by continuous subcutaneous infusion (3 to 11 mcg/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-formyl-methionyl-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 mcg/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 mcg/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 mcg/kg and 11.5 mcg/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 mcg/kg) and for subcutaneous administration (210 minutes, following filgrastim doses of 3.45 mcg/kg). Continuous 24-hour intravenous infusions of 20 mcg/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 mcg/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

Nivestym should be stored in the refrigerator at 2°C to 8°C. Do not store in the freezer. Store in the outer carton to protect from light.

Accidental exposure to room temperature (up to 25°C) or accidental exposure to freezing temperatures does not adversely affect the stability of the product. If frozen, thaw in refrigerator before administration. Discard Nivestym if frozen more than once.

Nivestym may be allowed to reach room temperature for a maximum of 15 days. Any prefilled syringe or vial left at room temperature for greater than 15 days should be discarded**.**

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

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

13 SPECIAL HANDLING INSTRUCTIONS

Nivestym should not be vigorously shaken.

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: $C_{845}H_{1339}N_{223}O_{243}S_9$

Molecular mass: Filgrastim consists of 175 amino acids with a molecular weight of 18,800 daltons.

Structural formula: Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is 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 in *E. coli*. Because filgrastim is produced in *E. coli*, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

Physical properties: pH of 3.8 – 4.3

Product Characteristics
Nivestym (filgrastim) is a sterile, clear, colorless, preservative-free liquid.

15 COMPARATIVE CLINICAL TRIALS

15.1 Comparative Trial Design and Study Demographics

Clinical studies conducted to support similarity between Nivestym and the reference biologic drug Neupogen included:

- An open-label, randomized, single-dose, crossover pharmacokinetic (PK) and pharmacodynamic (PD) study in healthy volunteers (C1121002).

- An open-label, randomized, multiple dose, crossover PD/PK study in healthy volunteers (C1121003).

- An open-label, randomized, multiple dose, parallel design, non-inferiority comparative immunogenicity study in healthy subjects (C1121012).

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in **Table 4**.

Table 4: Summary of trial design and patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
C1121002	A single center, open-label, randomized, single-dose, 2-way crossover, 2-period study in healthy volunteers assessing comparative PK, PD, safety, and immunogenicity	Nivestym 5 mcg/kg (480 mcg/0.8 mL in single-use prefilled syringes) US-Neupogen 5 mcg/kg (480 mcg/0.8 mL in single-use prefilled syringes) Single SC dose of either Nivestym or US-Neupogen in each of the 2 treatment periods, separated by at least a 28-day wash-out between periods.	n = 24 24 subjects received Nivestym 23 subjects received US-Neupogen	41.3 years (23-58)	Female: 11 (45.8%) Male: 13 (54.2%)
C1121003	A single center, open-label, randomized multiple-dose, 2-way crossover, 2-period study in healthy volunteers assessing comparative PD, PK, safety, and immunogenicity	Nivestym 5 mcg/kg (480 mcg/0.8 mL in single-use prefilled syringes) US-Neupogen 5 mcg/kg (480 mcg/0.8 mL in single-use prefilled syringes) Multiple SC doses of Nivestym or US-Neupogen in each of the 2 treatment periods separated by at least a 28 day washout between periods. Study drug was administered once daily for 5 consecutive days [Days 1-5] in Periods 1 and 2.	n = 60 59 subjects received at least 1 dose of Nivestym 58 subjects received at least 1 dose of US-Neupogen	44.0 years (23-63)	Female: 21 (35%) Male: 39 (65%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
C1121012	A multicenter, open-label randomized, 2-period, multiple-dose, parallel design non-interiority comparative immunogenicity study in healthy volunteers assessing immunogenicity and safety	Nivestym 5 mcg/kg (480 mcg/0.8 mL in single-use prefilled syringes) US-Neupogen 5 mcg/kg (480 mcg/0.8 mL in single-use prefilled syringes) Multiple SC doses of Nivestym or US-Neupogen administered once daily for 5 consecutive days in Period 1 [Days 1-5] and once in Period 2 [Day 1], with approximately 1 month between Day 1 of each treatment period.	n = 255 received study drug 128 subjects received at least 1 dose of Nivestym 127 subjects received at least 1 dose of US-Neupogen	37.65 (18-65)	Female: 129 (50.6%) Male: 126 (49.4%)
PK = Pharmacokinetic; PD = Pharmacodynamic; SC = Subcutaneous					

Study C1121002 was a single center, open-label, randomized, single-dose, 2-way crossover, 2-period study in healthy adult volunteers assessing comparative PK, PD, safety, and immunogenicity of Nivestym and US-Neupogen following a single dose of 5 mcg/kg body weight subcutaneous (SC) injection. The study evaluated 24 healthy subjects (n=12 in each treatment sequence Nivestym/US-Neupogen or US-Neupogen/Nivestym). One subject from the Nivestym/US-Neupogen treatment sequence did not complete the study, which resulted in 23 subjects being included in the statistical comparisons.

Study C1121003 was a single center, open-label, randomized, multiple-dose, 2-way crossover, 2-period study in healthy adult volunteers assessing comparative PK, PD, safety, and immunogenicity of Nivestym and US-Neupogen following multiple doses of 5 mcg/kg body weight SC injections. The study drugs were administered once daily for 5 consecutive days in each period of the study. The study evaluated 60 healthy subjects (n=30 in each treatment sequence Nivestym/US-Neupogen or US-Neupogen/Nivestym). Three subjects from the Nivestym/US-Neupogen treatment sequence and, one subject from the US-Neupogen/Nivestym treatment sequence did not complete the study, which resulted in 56 subjects being included in the statistical comparisons.

Study C1121012 was a multicenter, open-label randomized, 2-period, multiple-dose parallel non-inferiority comparative immunogenicity study evaluating the immunogenicity of multiple SC doses of Nivestym or US-Neupogen in healthy adult volunteers. Each subject were to receive 5 consecutive daily 5 mcg/kg doses of study drug during Period 1 [Days 1-5], and one dose in Period 2 [Day 1]. A total of 255 subjects who received at least 1 dose of either Nivestym (n=128) or US-Neupogen (n=127) were included in the statistical comparisons.

15.2 Comparative Study Results

15.2.1 Comparative Bioavailability Studies

15.2.1.1 Pharmacokinetics

Study C1121002 (single dose study in healthy volunteers)

The results of the pharmacokinetic comparisons are shown in **Table 5**.

Table 5: Study C1121002 - Analysis of Primary Pharmacokinetic Parameters

Filgrastim (1 x 5 mcg/kg/day) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-t} (hr•pg/mL)	243818.2 249801.3 (22.1)	214515.3 219551.5 (22.6)	114	105 - 123†
AUC_{0-inf} (hr•pg/mL)	244859.6 250801.4 (22.0)	215409.8 220438.3 (22.5)	114	105 - 123
C_{max} (pg/mL)	29630.7 30391.3 (23.4)	26628.3 27169.6 (20.9)	111	102 - 121†
T_{max}[3](hr)	6.0 (3.0 - 8.0)	6.0 (4.0 - 6.0)		
$T_{½}$[4] (hr)	2.8 (30.0)	2.9 (45.9)		

[1] Nivestym (filgrastim) by Pfizer.
[2] US-Neupogen (US-authorized Neupogen® (filgrastim)) by Amgen Inc., U.S.A.
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

AUC_{0-t} = area under the concentration versus time curve from time zero to the last measurable time point
AUC_{0-inf} = area under the serum filgrastim concentration curve from time zero to infinity
C_{max} = maximum serum concentration
T_{max} = time to maximum observed serum filgrastim concentration
$T_{½}$ = elimination half-life
†Acceptance Interval was 80.0% to 125.0%

Study C1121003 (multiple dose study in healthy volunteers)

The results of the pharmacokinetic comparisons are shown in **Table 6**.

Table 6: Study C1121003 - Analysis of Primary Pharmacokinetic Parameters

Filgrastim (5 mcg/kg/day x 5 consecutive days) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-24} (hr•pg/mL)	90885.7 95548.8 (33.1)	88840.4 94659.5 (37.2)	102	97 - 108†
AUC_{0-inf} (hr•pg/mL)	91626.8 96299.7 (33.0)	89667.0 95474.6 (37.0)	102	97 - 108
C_{max} (pg/mL)	15661.8 16630.4 (35.0)	15121.7 16219.6 (37.0)	103	95 - 112†
C_{trough} (pg/mL)[4]	133.3 (55.2)	135.6 (61.4)		
T_{max} (hr)[3]	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.0)		
$T_{1/2}$ (hr)[4]	3.7 (55.2)	4.0 (55.8)		

[1] Nivestym (filgrastim) by Pfizer
[2] US-Neupogen (US-authorized Neupogen® (filgrastim)) by Amgen Inc., U.S.A.
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean only

AUC_{0-24} = area under the serum filgrastim concentration curve from time zero to 24 hours on Day 5
C_{max} = maximum serum filgrastim concentration following filgrastim administration on Day 5
C_{trough}= serum filgrastim concentration prior to dose on Day 5
T_{max} = time to maximum observed serum filgrastim concentration
$T_{½}$ = elimination half-life following filgrastim administration on Day 5
†Acceptance Interval was 80.0% to 125.0%

15.2.1.2 Pharmacodynamics

Study C1121002 (single dose study in healthy volunteers)

The absolute neutrophil count (ANC) C_{max} (ANC_{max}) and AUC ($AUEC_{ANC}$) were assessed as pharmacodynamics endpoint parameters. The results of the pharmacodynamics comparisons are shown in **Table 7**.

Table 7: Study C1121002 - Analysis of Pharmacodynamic Parameters

ANC (1 x 5 mcg/kg/day filgrastim) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**%Ratio of Geometric Means**	**95% Confidence Interval**
$AUEC_{ANC}$ (10^3•hr/μL)	1241.5 1259.0 (16.8)	1247.3 1263.9 (16.8)	99	94 - 103†
ANC_{max} (10^3/μL)	21.4 21.9 (19.9)	21.9 22.3 (20.8)	98	92 - 104†

[1] Nivestym (filgrastim) by Pfizer
[2] US-Neupogen (US-authorized Neupogen® (filgrastim)) by Amgen Inc., U.S.A.

$AUEC_{ANC}$ = area under the effect ANC-time curve
ANC_{max} = maximum effect
ANC = absolute neutrophil count
†Acceptance Interval was 80.0% to 125.0%

Study C1121003 (multiple dose study in healthy volunteers)

The CD34+ count C_{max} ($CD34+_{max}$) and AUC ($AUEC_{CD34+}$) after last administration on Day 5 were assessed as pharmacodynamics endpoint parameters. The results of the pharmacodynamics comparisons are shown in **Table 8**.

Table 8: Study C1121003 - Analysis of Pharmacodynamic Parameters

$CD34^+$ (5 mcg/kg/day x 5 consecutive days filgrastim) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**%Ratio of Geometric Means**	**95% Confidence Interval**
$AUEC_{CD34^+}$ (cells•hr/μL)	3433.7 4374.8 (69.1)	3222.2 3939.2 (63.2)	106	97 – 117†
$CD34^+_{max}$ (cells/μL)	43.2 57.8 (83.1)	40.7 49.6 (61.6)	106	93 - 122†

[1] Nivestym (filgrastim) by Pfizer.
[2] US-Neupogen (US-authorized Neupogen® (filgrastim)) by Amgen Inc., U.S.A.

$AUEC_{CD34+}$ = area under the effect $CD34^+$-time curve
$CD34^+_{max}$ = maximum observed $CD34^+$ count
$CD34^+$ = hematopoietic progenitor cell antigen
†Acceptance Interval was 80.0% to 125.0%

15.2.2 Comparative Safety and Immunogenicity

15.2.2.1 Safety

The types, frequency and severity of adverse events were comparable between the biosimilar Nivestym and the reference biologic drug US-Neupogen in the 3 comparative clinical studies in healthy subjects with the 2 studies primarily assessing PD and PK and a third study primarily assessing immunogenicity.

15.2.2.2 Immunogenicity

A tiered approach was used for anti-filgrastim antibody (anti-drug antibody [ADA]) testing. A validated ECL bridging assay was used to test samples for the presence of ADA. Confirmed ADA positive test samples were further characterised by measurement of antibody titer in the ECL assay, testing by a cell-based neutralizing antibody (NAb) assay, and determination of antibody isotype by a SPR assay.

C1121002 (Single dose study in healthy volunteers)

In Study C1121002, serum was collected prior to dosing on Day 1, on Day 12 of each period, Day 28 of Period 1 and Day 28 of Period 2 (final visit) for ADA testing. Three subjects (12.5%) receiving US-Neupogen (Period 1)/Nivestym (Period 2) had a positive ADA result. Two of these subjects had a positive ADA result at baseline and of these 2 subjects, one remained ADA positive throughout the study. The third subject had a negative ADA result at baseline and positive ADA at all subsequent assessment time points. There was no evidence of a neutralizing response using a cell-based bioassay.

C1121003 (Multiple dose study in healthy volunteers)

In Study C1121003, blood samples were collected prior to dosing on Days 1, 12 and 33 of each period for ADA testing. One subject receiving Nivestym (Period 1)/US-Neupogen (Period 2) was observed positive for ADA at Period 1, Day 33. The subject's ADA result was negative at Period 2, Day 1. This ADA positive sample was negative for NAb testing.

C1121012 (Non-inferiority Immunogenicity study in healthy volunteers)

In Study C1121012, blood samples for immunogenicity assessment were collected during Period 1 on Days 0, 10 and 26, and during Period 2 on Days 0, 10 and 31 (final visit). A total of 15 subjects had a confirmed positive treatment-emergent ADA result, at least once during the study (9 subjects [7.4%] in the Nivestym group and 6 subjects [4.9%] in the US-Neupogen group). Non-inferiority was established, as the upper limit of the 95% CI was ≤ 10% for the total of 15 subjects with confirmed positive ADA results. There was no evidence of NAb for any subject.

Additionally, there was no evidence of increased antibody titer upon administration of additional doses of study drug, including in Period 2, which followed a window in time to allow the opportunity for antigen rechallenge. There were no clinical manifestations of antibody formation, such as either hypersensitivity reactions or decreased ANC after completion of the treatment period.

16 COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

16.1 Comparative Non-Clinical Pharmacodynamics

In vitro Studies

Filgrastim binds to the G-CSF receptor on the surface of myeloid progenitor cells and stimulates granulocyte production. The functional activity of Nivestym was compared to Neupogen using several *in vitro* assays, which reflect its mechanism of action of stimulation of proliferation of specific cell populations after receptor binding (**Table 9**).

Table 9: Comparison of Functional Activity between Nivestym and Neupogen

Assay	Test	Key Findings
In vitro cell-based bioassay	Proliferation of M-NFS-60 cells	The in vitro potencies were comparable between Nivestym and Neupogen.
Binding assay	Competitive receptor binding assay	The relative binding affinities of Nivestym and Neupogen to the G-CSF receptor were shown to be comparable.
Receptor binding affinity	Surface plasmon resonance	The relative binding affinities of Nivestym and Neupogen to the G-CSF receptor were comparable.

The potency of Nivestym was compared to Neupogen in an *in vitro* cell-based bioassay which measures the proliferation of a myeloid progenitor cell line, M-NFS-60. A competitive receptor binding assay was performed to assess the relative binding of Nivestym and Neupogen to the G-CSF receptor. The binding affinity of Nivestym and Neupogen to the G-CSF receptor was evaluated using surface plasmon resonance. The results of the *in vitro* assays associated with the mechanism of action of filgrastim demonstrated comparability between Nivestym and Neupogen.

16.2 Comparative Toxicology

Nivestym is a biosimilar where the animal toxicology properties of filgrastim have already been characterized for the reference biologic drug (See Part II, section 18, **NON-CLINICAL TOXICOLOGY – REFERENCE BIOLOGIC DRUG**). Rats exposed to 20 or 500 mcg/kg of Nivestym or US-Neupogen repeated (once daily) subcutaneous injections up to 4 weeks, displayed comparable toxicological profiles. No unexpected toxicities were identified for Nivestym.

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 mcg/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 10^9/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 mcg/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 x 10^9/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 mcg/kg/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 x 10^9/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 x 10^9/L) and moderate (ANC < 1.0 x 10^9/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 mcg/kg/day, given as a continuous infusion on days 4 through 17 of a 21-day chemotherapy cycle.

Sixty-three pediatric patients with advanced neuroblastoma or 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, multicenter, 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 10^9/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 mcg/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 10^9/L) occurred in the filgrastim-treated group versus the control group [23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/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 mcg/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 mcg/kg/day group, and 5.5 days in the 20 mcg/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 or non-myeloid malignancies were treated with myeloablative therapy and allogeneic bone marrow transplant followed by 300 mcg/m^2/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 $\geq 0.5 \times 10^9$/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 or 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 leukemia (ALL), or germ cell tumor. In these studies, the recovery of the ANC to $\geq 0.5 \times 10^9$/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 hematopoietic 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 hemorrhagic complications and the need for platelet transfusions.

Filgrastim Mobilized PBPC Collection

In 4 studies (n = 126), patients with NHL, HD, ALL, or breast cancer received filgrastim for 6 to 7 days to mobilize hematopoietic 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 hematologic recovery. Long-term (limited to 100 days) follow up hematology data from patients treated with PBPCT 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 or idiopathic neutropenia were evaluated. Untreated patients had a median ANC of 0.210 x 10^9/L. Filgrastim therapy was adjusted to maintain the median ANC between 1.5 x 10^9/L and 10 x 10^9/L. A complete response was seen in 88% of patients (defined as a median ANC 1.5 x 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 x 10^9/L (range 0.03 to 30.88 x 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 mcg/kg/day) than for patients with idiopathic (0.6 to 11.5 mcg/kg/day) or cyclic (0.5 to 6 mcg/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 x 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 x 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 x 10^9 and 10 x 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, non-comparative 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 mcg/kg/animal (862.5 mcg/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 mcg/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 hematopoietic 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 osteoclasis and osteoanagenesis in the hind legs (which account for 30% of hematopoiesis 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 mcg/kg, 5 of 8 (4 males and 1 female) monkeys given r-metHuG-CSF at 1,150 mcg/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 hemorrhagic 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 mcg/kg.

No hamsters or dogs died following 14 days of intravenous r-metHuG-CSF administration at doses up to 34.5 mcg/animal (equivalent to 213.9 mcg/kg based on group mean pre-study body weights) and 345 mcg/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 mg/kg/day and death was associated with a gross exaggeration of granulopoietic activity.

19 SUPPORTING PRODUCT MONOGRAPHS

1 PrNeupogen® (Solution for Injection, 300 mcg/mL & 600 mcg/mL, submission control 212959, Product Monograph, Amgen Canada Inc. April 10, 2018

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]Nivestym[TM] (pronounced) <Neye-vest-im>
(filgrastim injection)

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

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

Serious Warnings and Precautions

- The spleen may become enlarged and can rupture while taking Nivestym. A ruptured spleen can cause death. Call your doctor right away if there is 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 Nivestym 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 Nivestym, resulting in death in some cases.

What is Nivestym used for?

Nivestym 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 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 Nivestym work?

Nivestym is a man-made form of granulocyte colony-stimulating factor (G-CSF), which is made using a type of *E coli* bacteria. G-CSF is a substance naturally produced by the body. It stimulates the growth of neutrophils (**nu**-tro-fils), which are a type of white blood cell important in the body's fight against infection. Nivestym works by helping your body make more neutrophils. To make sure Nivestym 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 Nivestym?

Medicinal ingredients: filgrastim
Non-medicinal ingredients: acetate, polysorbate 80, sodium, sorbitol, and water

Nivestym comes in the following dosage forms:

Prefilled Syringes (600 mcg/mL)

- 300 mcg/0.5 mL in a single-use graduated prefilled syringe with a BD Ultrasafe Plus[TM] Passive Needle Guard

- 480 mcg/0.8 mL in a single-use graduated prefilled syringe with a BD Ultrasafe Plus™ Passive Needle Guard

The Nivestym syringe plunger stopper and needle cover are not made with natural rubber latex.

Vials (300 mcg/mL)
- 300 mcg/1 mL in a single-use vial
- 480 mcg/1.6 mL in a single-use vial

The vial stopper is not made with natural rubber latex.

Do not use Nivestym if:
- You are allergic (hypersensitive) to filgrastim or any of the other ingredients. For a detailed list of medicinal and non-medicinal ingredients, see above "**What are the ingredients in Nivestym?**".
- 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 Nivestym. 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).
- 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.

Other warnings you should know about:

Nivestym may reduce your chance of getting an infection, but does not prevent all infections. An infection can still happen during the short time when you/your child's neutrophil levels are low. You must be alert and look for some of the common signs or symptoms of infection, such as fever, chills, rash, sore throat, diarrhea, or redness, swelling, or pain around a cut or sore. If you/your child has any of these signs or symptoms during treatment with Nivestym, tell your doctor or nurse immediately.

There is a possibility that you could have a reaction at an injection site. If there is a lump, swelling, or bruising at an injection site that does not go away, call your doctor.

If you have a sickle cell trait or sickle cell disease, make sure that you tell your doctor before you start taking Nivestym. If you have a sickle cell crisis after getting Nivestym, tell your doctor right away.

Make sure your doctor knows about all medicines, and herbal or vitamin supplements you are taking before starting Nivestym. If you are taking lithium you may need more frequent blood tests.

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

Talk to your doctor if you experience unusual bleeding or bruising while taking Nivestym following chemotherapy, as this could mean a decrease of platelets which reduces the ability of blood to clot.

If you have any questions, you should talk to your doctor.

What about pregnancy or breastfeeding?
Nivestym has not been studied in pregnant women, and its effects on unborn babies are not known. If you take Nivestym while you are pregnant, it is possible that small amounts of it may get into your baby's blood. It is not known if Nivestym can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breastfeeding, you should tell your doctor before using Nivestym.

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 Nivestym:
Interactions between Nivestym and other drugs have not been studied. Drugs such as lithium may affect the release of neutrophils into the blood stream. You should discuss your treatment with your doctor before using Nivestym if you are currently on lithium treatment.

How to take Nivestym:

If you or your child are/is receiving Nivestym while receiving chemotherapy, the first dose should be given at least 24 hours after the chemotherapy and the last dose of Nivestym 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 you/your child's body weight.

Overdose:
You must always use the correct dose of Nivestym. Too little Nivestym may not protect against infections, and too much Nivestym may cause too many neutrophils to be produced and be found in blood.

If you think you or your child have/has received too much Nivestym, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Nivestym should be injected at the same time each day. If a dose is missed, contact your doctor or nurse.

Information on How to Inject Nivestym:
Detailed instructions on how to inject Nivestym are provided in **"Instructions for Use". It is important that you do not try to give the injection unless you have received training from your doctor or nurse.**

You should not inject a dose of Nivestym of less than 0.3 mL from a Nivestym graduated prefilled single-use syringe. A dose of less than 0.3 mL cannot be accurately measured using the Nivestym prefilled single-use syringe.

What are possible side effects from using Nivestym?

These are not all the possible side effects you or your child may experience when taking Nivestym. If you or your child experience any side effects not listed here, contact your healthcare professional.

- **Spleen Rupture.** The spleen may become enlarged and can rupture while taking Nivestym. A ruptured spleen can cause death. The spleen is located in the upper left section of the belly or 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.** Nivestym can cause serious allergic reactions. These reactions can cause a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating. If you or your child starts to have any of these symptoms, stop using Nivestym and call your doctor or seek emergency care right away. If you or your child has an allergic reaction during the injection of Nivestym, 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 bones, chest, gut or joints.
- **Kidney injury (glomerulonephritis)** Call your doctor right away if you or your child experience puffiness of the face or ankles, blood in the urine or brown colored urine, or if you notice that you or your child urinate less often than usual.

Most common side effects of Nivestym
The most common side effect you or your child may experience is bone, joint and/or muscle pain. This pain can usually be relieved by taking a non-acetylsalicylic acid (non-aspirin) 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 experience a lump, redness, swelling, bruising or itching at the site of injection. This may be an allergy to the ingredients in Nivestym or it may be a local reaction. If you notice any signs of a local reaction, call your doctor. **If at any time a serious allergic reaction occurs, immediately call a 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)		√	
UNCOMMON ≥ 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		√	√

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	
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-colored, 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 or your child have/has 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 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 Nivestym after the expiry date which is stated on the outer carton and the label of the prefilled syringe and the vial.

- Nivestym should be stored in the refrigerator between 2˚C to 8˚C but not in the freezer. Avoid shaking.
- If Nivestym 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.
- Nivestym can be left out at room temperature (not above 25ºC) for a single period of up to 15 days that ends within the labeled expiry date. Once Nivestym has been out at room temperature, it should not be place back into the refrigerator. Any Nivestym syringes or vials 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 Nivestym in the outer carton to protect from light or physical damage. Do not leave Nivestym in direct sunlight. Do not use if you notice it is cloudy or there are particles in it.
- If you have any questions about storage or how to carry Nivestym when you travel, contact your doctor, nurse, or pharmacist.

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 Nivestym:

- 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); the manufacturer's website at www.pfizer.ca or by calling Pfizer Canada ULC at: 1-800-463-6001.

This leaflet was prepared by:
Pfizer Canada ULC
Kirkland, Québec H9J 2M5

Last Revised: February 05, 2019

Instructions for Use

PrNivestym™ (Neye-vest-im)

(filgrastim injection)

Single-use Graduated Prefilled Syringe

Important

Read the Patient Medication Information for important information you need to know about Nivestym before following this Instructions for Use.

Before you use a Nivestym prefilled syringe, read this important information.

Storing your Nivestym prefilled syringe

- Store the Nivestym prefilled syringe in the refrigerator between 2°C to 8°C.
- **Do not freeze.**
- Keep the Nivestym prefilled syringe in the original carton to protect from light or physical damage.
- Take the Nivestym prefilled syringe out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- The Nivestym prefilled syringe may be allowed to reach room temperature for up to 15 days. **Throw away (dispose of) any Nivestym prefilled syringe that has been left at room temperature for longer than 15 days.**
- After you inject your dose, throw away (dispose of) any unused Nivestym left in the prefilled syringe. **Do not** save unused Nivestym in the prefilled syringe for later use.
- **Keep the Nivestym prefilled syringe and all medicines out of the reach of children.**

Using your Nivestym prefilled syringe

- **It is important that you do not try to give the injection unless you or your caregiver has received training from health care provider.**
- Make sure the name Nivestym appears on the carton and prefilled syringe label.
- **Do not** use a Nivestym prefilled syringe after the expiration date on the label.
- **Do not** shake the Nivestym prefilled syringe.
- **Do not** use the prefilled syringe if the medicine is cloudy or discolored or contains flakes or particles.
- The prefilled syringe has a needle guard that needs to be activated to cover the needle after the injection is given. The needle guard will help prevent needle stick injuries to anyone who handles the prefilled syringe.
- **Do not** remove the needle cover from the prefilled syringe until you are ready to inject**.**
- **Do not** use a Nivestym prefilled syringe if the needle cover is missing.
- **Do not** use the prefilled syringe if the carton is open or damaged.
- **Do not** use a prefilled syringe if it has been dropped on a hard surface. The prefilled syringe may be broken even if you cannot see the break. Use a new prefilled syringe.

Call your healthcare provider if you have any questions.

About the Nivestym prefilled syringe

- Nivestym prefilled syringes come in two strengths. Depending on your prescription, you will receive Nivestym prefilled syringes that contain 300 mcg/0.5mL or 480 mcg/0.8mL of medicine. Your healthcare provider will determine the dose in milliliters (mL) that you will need to give based on your body weight.
- **You should not inject a dose of Nivestym less than 0.3 mL (180 mcg) from a Nivestym prefilled syringe. A dose less than 0.3 mL cannot be accurately measured using the Nivestym prefilled syringe.**
- When you receive your Nivestym prefilled syringes, always check to see that the:
  - name Nivestym appears on the carton and prefilled syringe label.
  - expiration date on the prefilled syringe label has not passed. **You should not use a prefilled syringe after the date on the label.**
  - strength of Nivestym (number of micrograms on the carton containing the Nivestym prefilled syringe) is the same as what your healthcare provider prescribed.

Nivestym prefilled syringe parts (see Figure A).

Nivestym 300 mcg/0.5mL prefilled syringe is shown as an example.

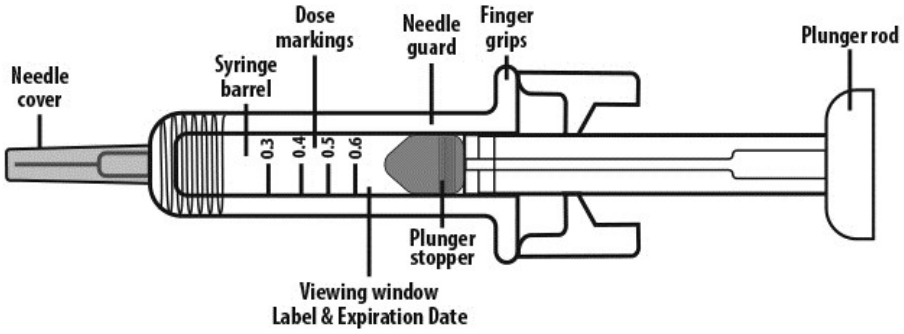

Figure A

What you need for your injection

Included in the carton:

- 1 new Nivestym prefilled syringe

Not included in the carton (see Figure B)

- 1 adhesive bandage
- 1 alcohol wipe
- 1 cotton ball or gauze
- sharps disposal container

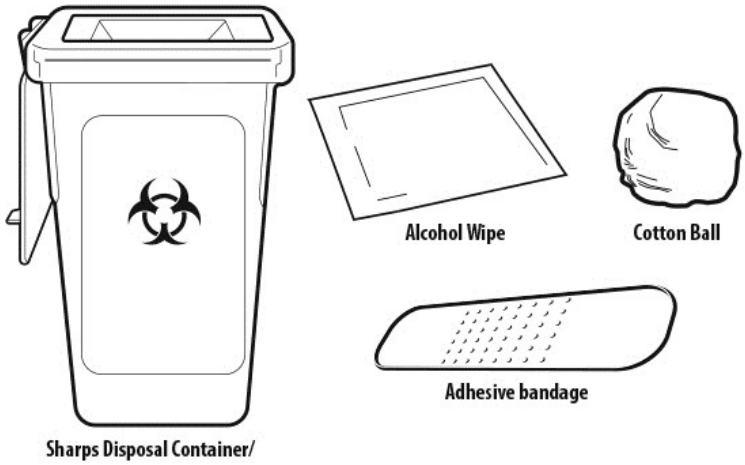

Figure B

Figure C shows a needle guard that has not yet been activated. The prefilled syringe is ready for use. This is what the prefilled syringe looks like before use.

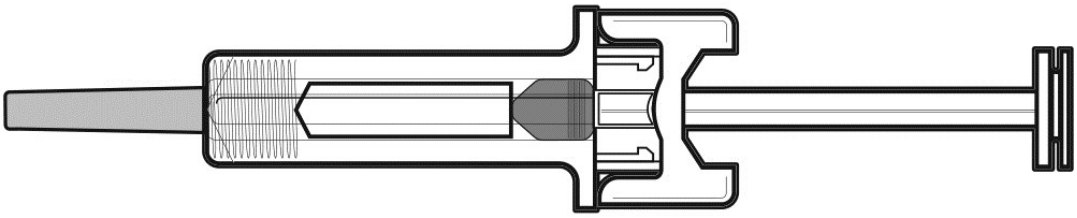

Figure C

Figure D shows a needle guard that has been activated. This is what the prefilled syringe looks like after use.

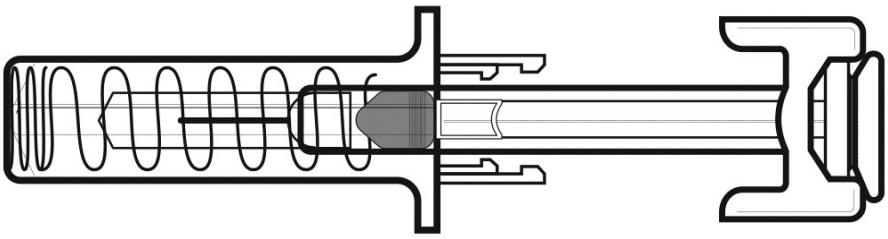

Figure D

Preparing the Nivestym prefilled syringe

Step 1: Find a clean, well-lit flat work surface.

Step 2: Take the carton containing the Nivestym prefilled syringe out of the refrigerator and leave it **unopened** on your work surface for at least **30** minutes so that it reaches room temperature. Put the original carton with any unused prefilled syringes back in the refrigerator.

- **Do not shake the prefilled syringe.**
- **Do not leave the prefilled syringe in direct sunlight.**

Step 3: Wash your hands with soap and water.

Step 4: Remove the prefilled syringe from the carton. Check to make sure that the needle guard is covering the barrel of the syringe. **Do not push the needle guard over the needle cover before the injection.** This may activate or lock the needle guard. See Figure C above that shows how the prefilled syringe looks before use.

If the needle guard is covering the needle that means it has been activated. See Figure D above that shows how the prefilled syringe looks after use. **Do not use the Nivestym prefilled syringe.** Get another prefilled syringe that has not been activated and is ready to use.

Step 5: Check the expiration date on the Nivestym prefilled syringe. **Do not use the Nivestym prefilled syringe if the expiration date has passed.**

Step 6: Inspect the medicine and prefilled syringe. Turn the prefilled syringe so you can see the medicine and markings in the window. Look through the window on the Nivestym prefilled syringe. Make sure the medicine in the prefilled syringe is clear and colorless.

- **Do not use the Nivestym prefilled syringe if:**
  - The medicine is cloudy or discolored, or contains flakes or particles.
  - Any part of the prefilled syringe appears cracked or broken.
  - The prefilled syringe has been dropped.
  - The needle cover is missing or not securely attached.
  - The expiration date printed on the label has passed.

- In all cases, use a new prefilled syringe and call your healthcare provider.

Step 7: Choose the injection site.

- When giving your injections, follow your healthcare provider's instructions about changing the site for each injection. Areas of your body that you may use as injection sites include (See Figure E):
  - front of your thighs
  - stomach area (abdomen), except for a **2-**inch area around your navel (belly button)
  - outer upper arms, only if a caregiver is giving you the injection.
  - upper outer areas of the buttocks, only if a caregiver is giving you the injection.

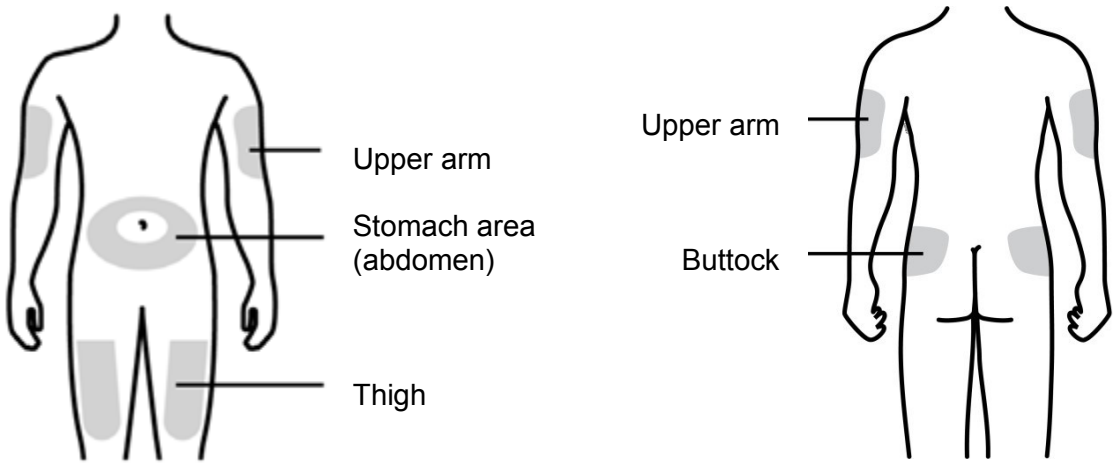

Figure E

- Choose a different site for each injection of Nivestym.
- **Do not** inject into areas where the skin is tender, red, bruised, or hard. Avoid injecting into areas with scars or stretch marks.

Step 8: Clean your injection site with an alcohol wipe. See Figure F.

- Let your skin dry.
- **Do not** touch this area again before injecting.

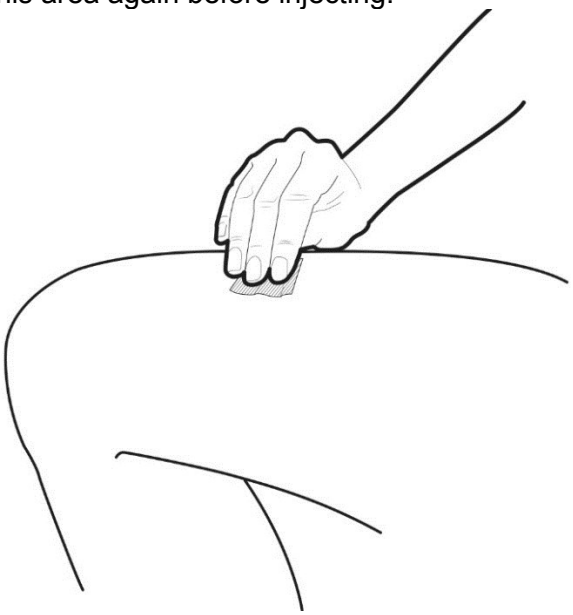

Figure F

Step 9: Hold the prefilled syringe by the needle guard with the needle cover pointing up. Carefully pull the needle cover straight off and away from your body. Throw away the needle cover. **Do not recap the needle.** See Figure G.

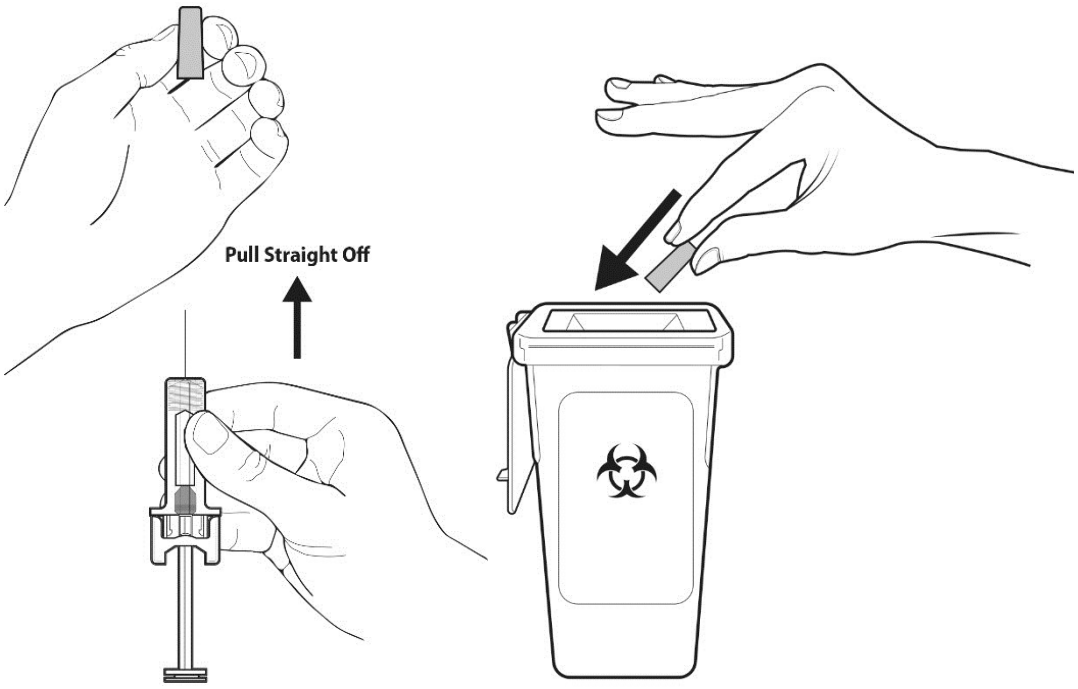

Figure G

Your healthcare provider has prescribed either a “full” syringe dose or a “partial” syringe dose.

- If you are prescribed a partial dose of Nivestym, follow Steps 10 through 18.
- If you are prescribed a full dose, you will inject **all** of the medicine from your prefilled syringe. For a full dose, skip Steps 10 and 11, and follow Steps 12 through 18.

Partial dosing

Step 10: Point the needle up and tap gently until the air rises to the top. See Figure H.

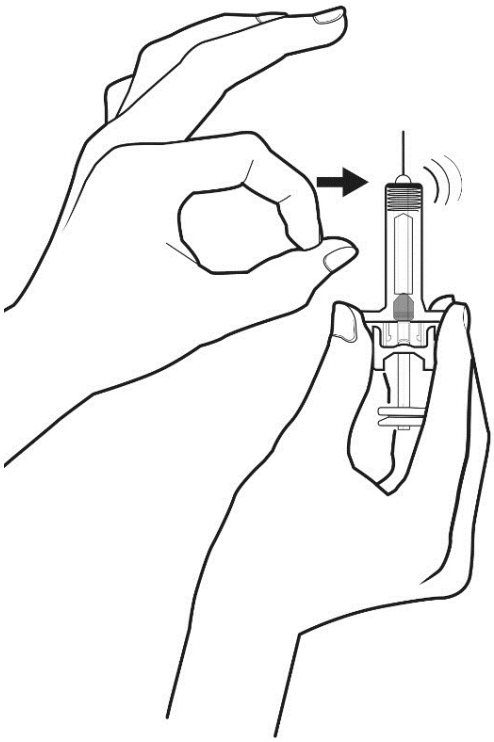

Figure H

Step 11: Holding the prefilled syringe as shown, slowly push up on the plunger rod to push out the extra air and medicine until the end of the conical base (edge) of the plunger stopper lines up with the syringe marking for your prescribed dose. See Figure I for an example of a dose of 0.3 mL. Your dose may be different than the example shown here.

Be careful not to activate the needle guard before use. **Do not use a Nivestym prefilled syringe that has been activated.**

Check again to make sure the correct dose of Nivestym is in the prefilled syringe.

You should not inject a dose of Nivestym less than 0.3 mL (180 mcg) from a Nivestym prefilled syringe. A dose less than 0.3 mL cannot be accurately

measured using the Nivestym prefilled syringe.

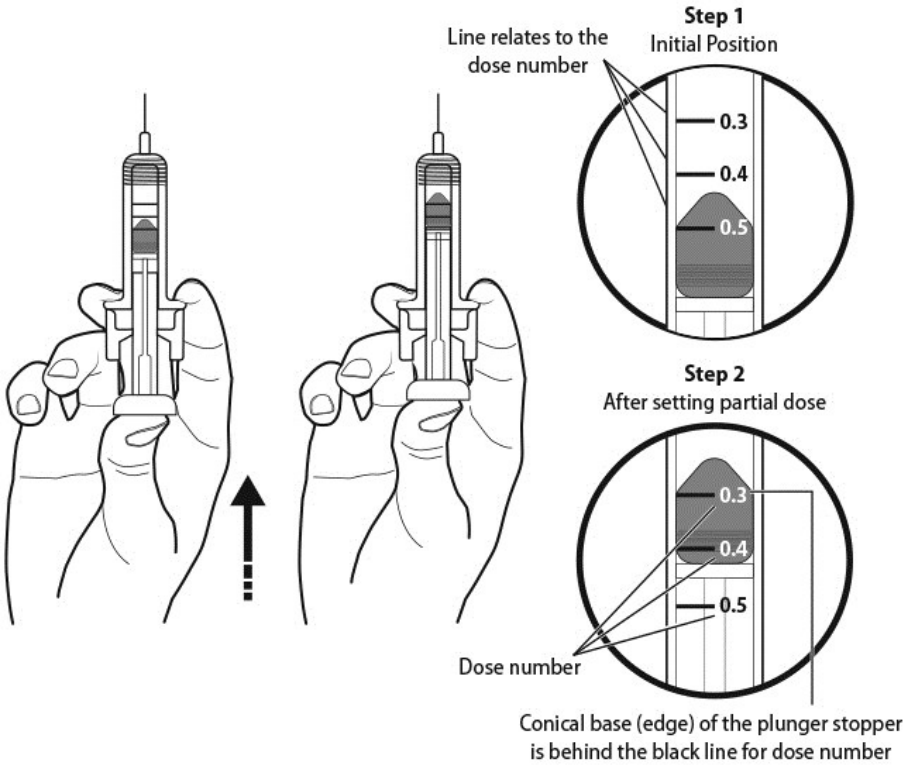

Figure I

Administering the Nivestym prefilled syringe

Step 12: With one hand, gently pinch a fold of skin at the injection site. Hold the pinch. See Figure J.

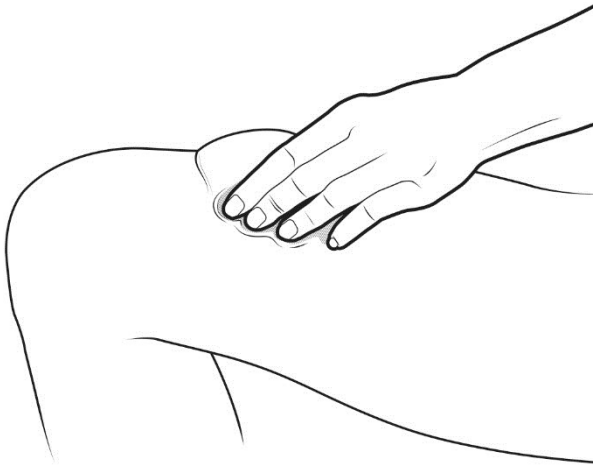

Figure J

Step 13: With your other hand, hold the prefilled syringe like you would hold a pencil. Use a quick “dart-like” motion to insert the needle into the skin at a 45 to 90 degree angle as

shown. See Figure K.

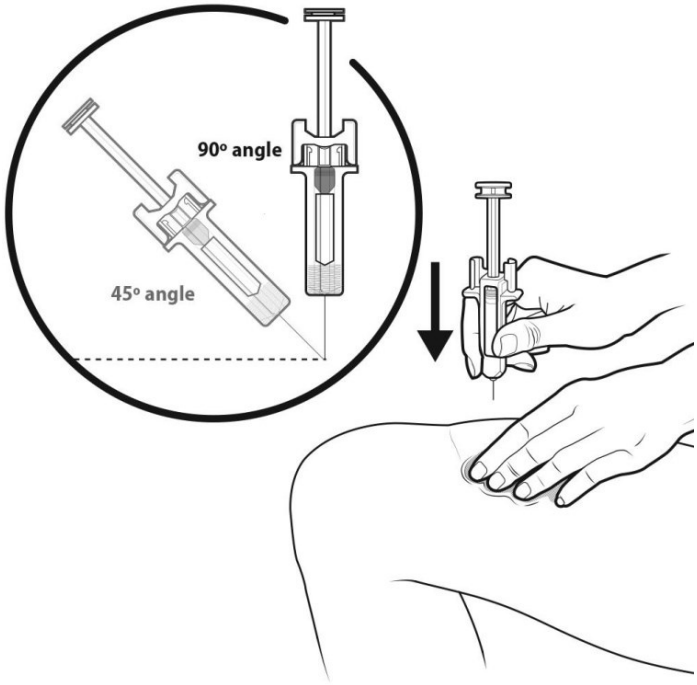

Figure K

Step 14: Using a slow and constant pressure, press down on the plunger rod as far as it will go. Keep the plunger rod fully pressed down while you hold the syringe in place for 5 seconds. See Figure L.

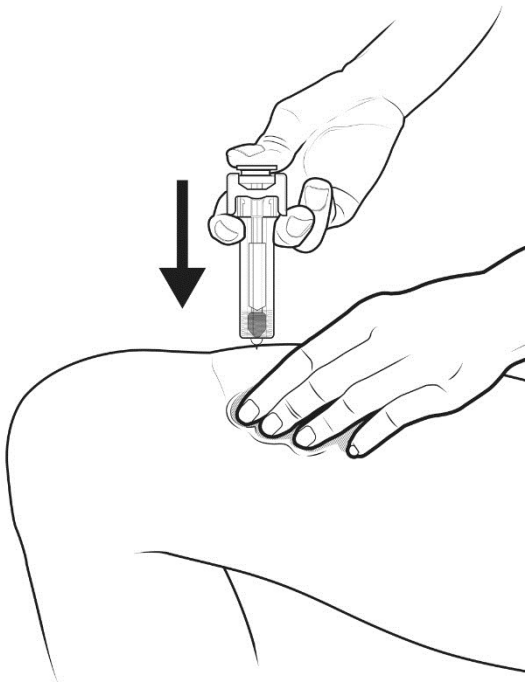

Figure L

Step 15: Keep the plunger rod fully pressed down while you carefully pull the needle straight out from the injection site. See Figure M.

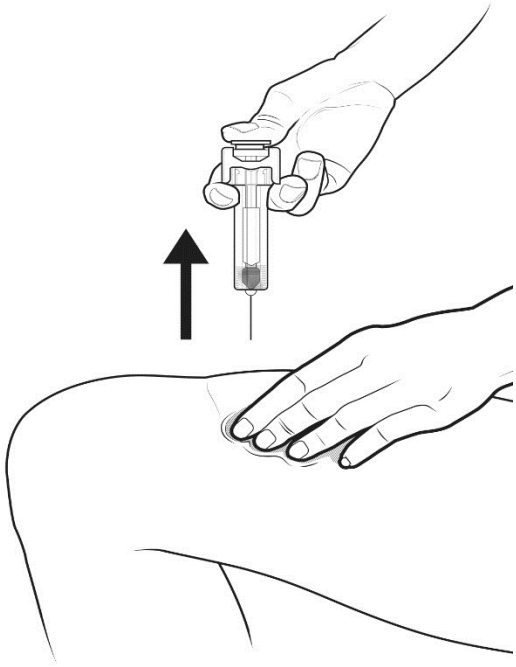

Figure M

Step 16: As you let go of the plunger rod, the needle guard will automatically slide over the needle until the needle is completely covered and the needle guard locks into place. **Do not recap the needle.** See Figure N.

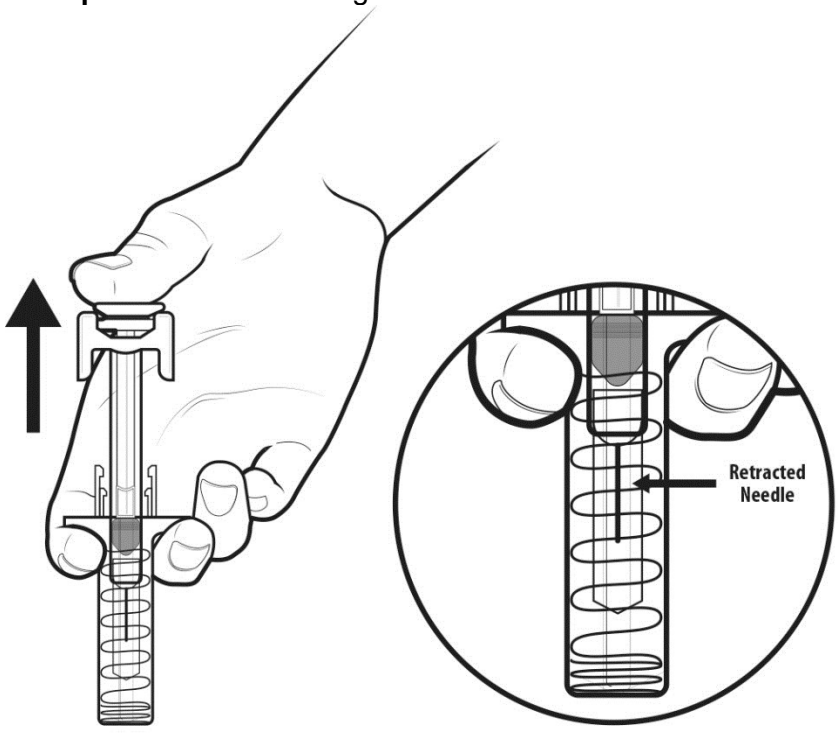

Figure N

Step 17: There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. **Do not** rub the injection

site**.** You may cover the injection site with a small adhesive bandage, if needed. See Figure O.

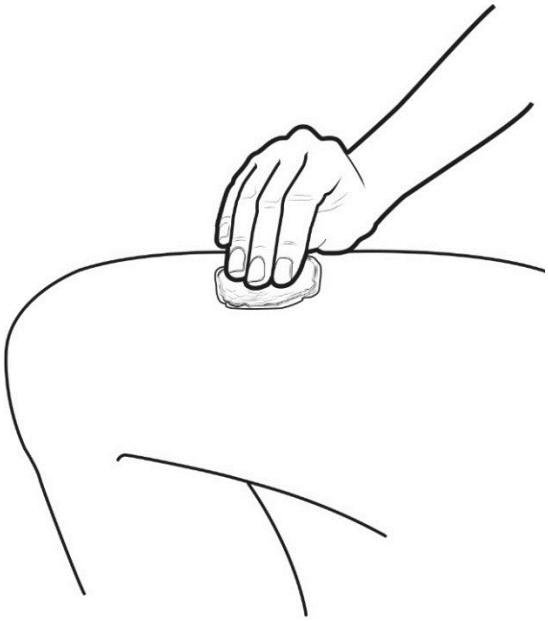

Figure O

Step 18: Throw away (dispose of) the syringe as instructed by your healthcare provider or by following the instructions below. There may be special provincial or local laws for disposal of used needles and syringes. See Figure P.

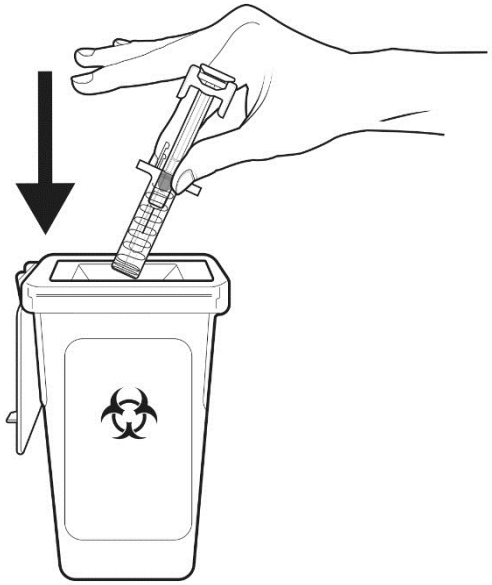

Figure P

How should I dispose (throw away) used Nivestym prefilled syringes?

- Put your used prefilled syringe in a sharps disposal container right away after use. **Do not throw away (dispose of)** syringes in your household trash.
- **Always keep the sharps disposal container out of the reach of children.**
- If you do not have a sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant and,
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be special provincial or local laws for disposal of used needles and syringes.
- Do not dispose of your used sharps container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

This Instructions for Use was prepared by:
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Last Revised: February 05, 2019

Instructions for Use

PrNivestym™ (Neye-vest-im)

(filgrastim injection)

Single-use Vial

Important

Read the Patient Medication Information for important information that you need to know about Nivestym following these Instructions for Use.

Before you use a Nivestym vial, read this important information.

Storing your Nivestym vial

- Store the Nivestym vial in the refrigerator between 2˚C to 8˚C.
- **Do not freeze.**
- Keep the Nivestym vial in the original carton to protect from light or physical damage.
- Take the Nivestym vial out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- The Nivestym vial may be allowed to reach room temperature for up to 15 days. **Throw away (dispose of) any Nivestym vial that has been left at room temperature for longer than 15 days.**
- After you inject your dose, throw away (dispose of) any unused Nivestym left in the vial. **Do not** save unused Nivestym in the vial for later use.
- **Keep Nivestym vial and all medicines out of the reach of children.**

Using your Nivestym vial

- **It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider.**
- Make sure the name Nivestym appears on the carton and vial label.
- **Only use the vial 1 time. Discard (throw away) the vial with any remaining Nivestym liquid.**
- **Do not** use a Nivestym vial after the expiration date on the label.
- **Do not** shake the Nivestym vial.
- **Do not** use the vial if the medicine is cloudy or discolored or contains flakes or particles.

Call your healthcare provider if you have any questions.

About the Nivestym vial

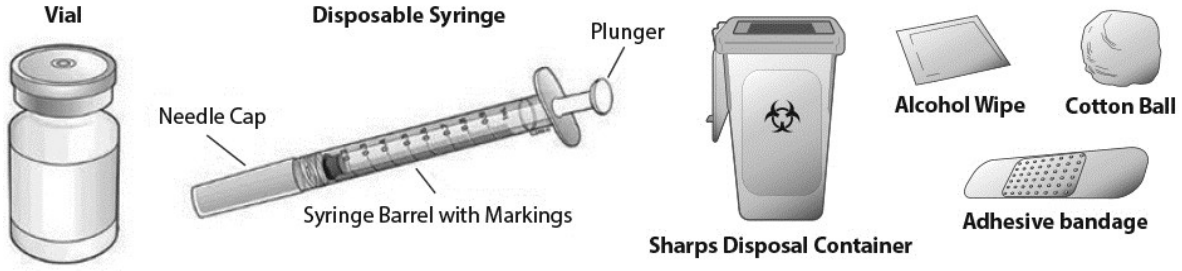
- Nivestym single-use vials come in two strengths. Depending on your prescription, you will receive Nivestym single-use vial that contain 300 mcg/1 mL or 480 mcg/1.6 mL of medicine. Your doctor will determine the dose in milliliters (mL) that you will need to give based on your body weight.

- When you receive your Nivestym vials, always check to see that the:
  - name Nivestym appears on the carton and Nivestym vial label.
  - expiration date on the Nivestym vial label has not passed. **You should not use a Nivestym vial after the date on the label.**
  - strength of Nivestym (number of micrograms on the carton containing the Nivestym vial) is the same as what your doctor prescribed.

What you need for your injection

Included in the carton:
- 1 new Nivestym single-use vial

Not included in the carton:
- 1 disposable syringe and needle
- 2 alcohol wipes
- 1 cotton ball or gauze pad
- 1 adhesive bandage
- Sharps disposal container



- Only use the disposable syringes and needles that your healthcare provider prescribes.
- Only use the syringes and needles 1 time. Throw away (dispose of) any used syringes and needles. See Step 9 - Finish, for instructions about how to properly dispose of used syringes and needles.
- You should only use a syringe that is marked in tenths of milliliters (mL).
- Your healthcare provider will show you how to measure the correct dose of Nivestym. This dose will be measured in milliliters (mL).

Preparing the Nivestym vial

Step 1: Remove the vial from the refrigerator. Find a clean, well-lit flat work surface.

Step 2: Place the vial on your clean work surface for 30 minutes and allow it to reach room temperature before you give an injection.

- **Do not** try to warm the vial by using a heat source such as hot water or microwave.
- **Do not leave the vial in direct sunlight.**
- **Do not** shake the vial.
- Use the vial only 1 time.

Step 3: Wash your hands thoroughly with soap and water.

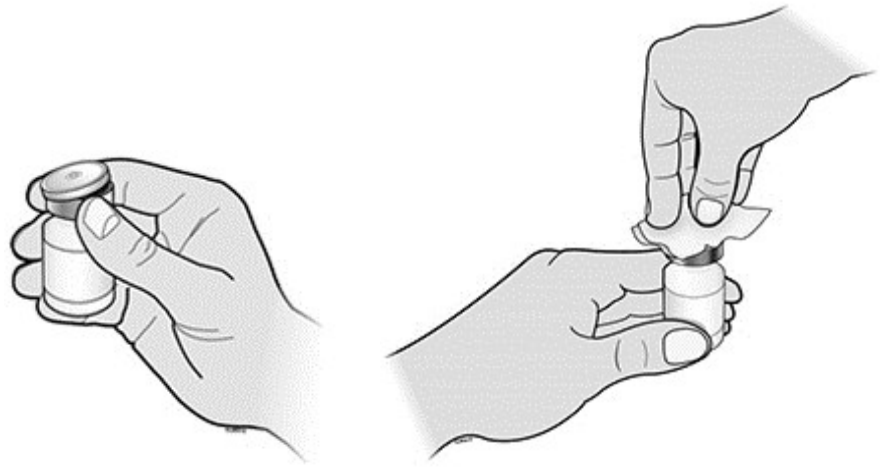
Step 4: Inspect the vial

Make sure the medicine in the vial is clear and colorless.

- **Do not** use the vial if:
  - The medicine is cloudy or discolored or contains flakes or particles.
  - The expiration date printed on the label has passed.
- In all cases, use a new vial and call your healthcare provider.

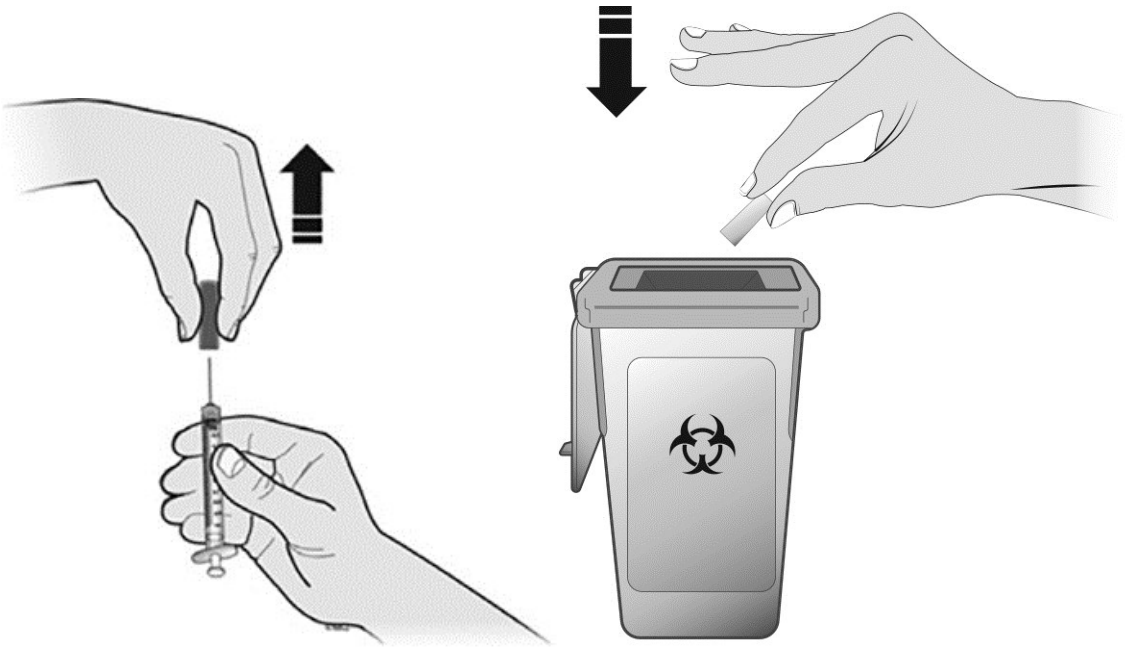
Step 5: Get Ready

A Take the cap off the vial. Clean the rubber stopper with 1 alcohol wipe.



B Check the carton containing the needle and syringe. If the carton has been opened or damaged, do not use that needle and syringe. Dispose of (throw away) that needle and syringe in the sharps disposal container.

C Hold the syringe by the barrel with the needle cap pointing up. Carefully pull the needle cap straight off and away from your body.

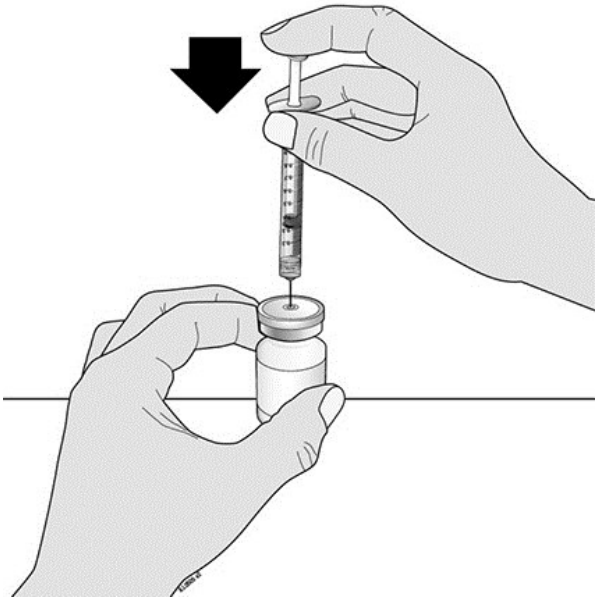


Pull back on the plunger and draw air into the syringe that is the same amount (mL) as the dose of Nivestym that your healthcare provider prescribed.

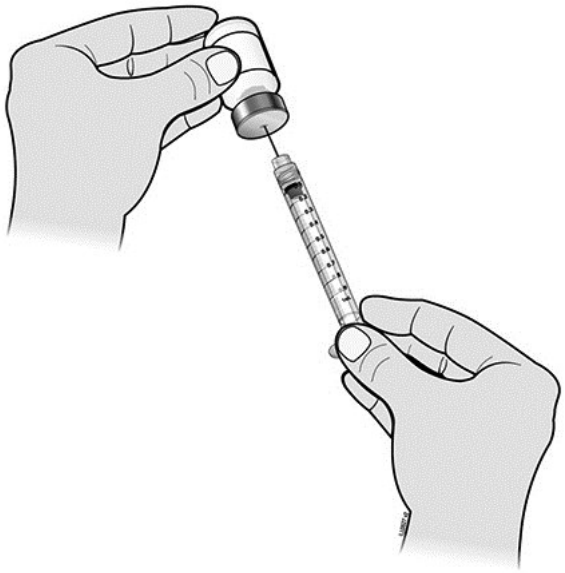
Important: Throw away the needle cap into the sharps disposal container. Do not recap the needle.

D Keep the vial on the flat work surface and insert the needle straight down through the rubber stopper. Do not insert the needle through the rubber stopper more than 1 time.

E Push the plunger down and inject all the air from the syringe into the vial of Nivestym.

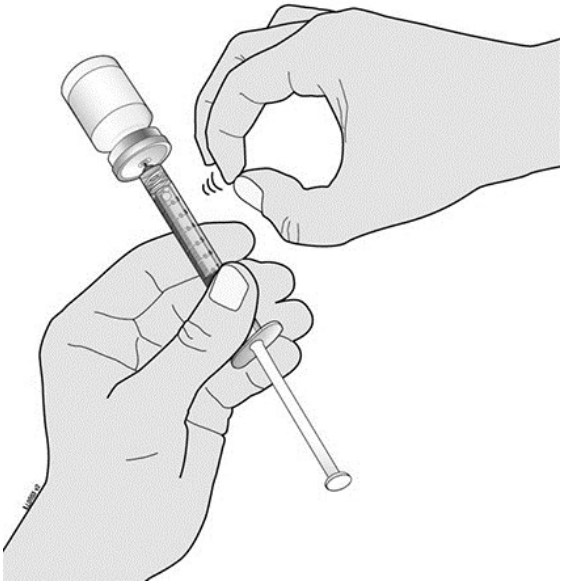


F Keep the needle in the vial and turn the vial upside down. Make sure that the Nivestym liquid is covering the tip of the needle.



G Keep the vial upside down and slowly pull back on the plunger to fill the syringe barrel with Nivestym to the correct marking amount (mL) of medicine that matches the dose your healthcare provider prescribed.

H Keep the needle in the vial and check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe barrel with your finger until the air bubbles rise to the top. Slowly push the plunger up to push the air bubbles out of the syringe.



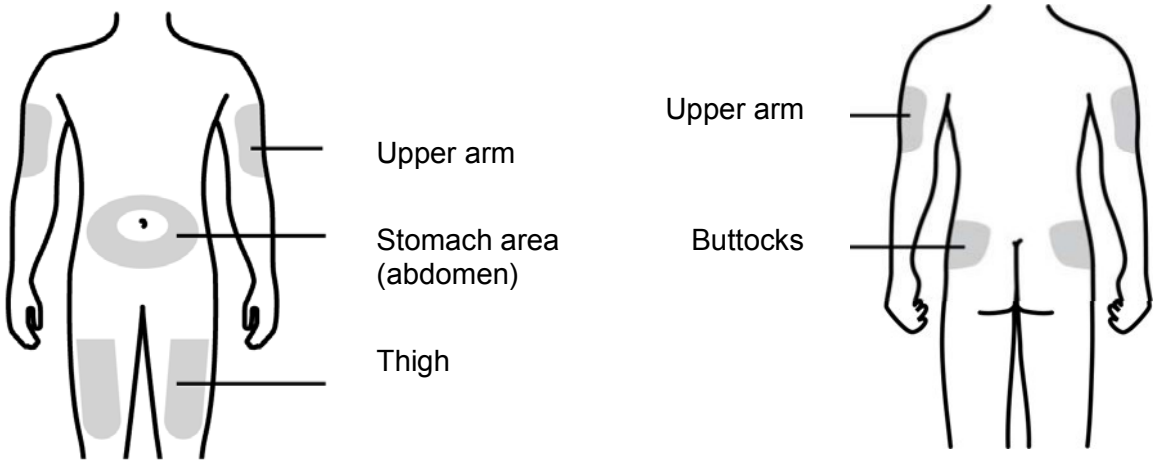
I Keep the tip of the needle in the liquid and again pull the plunger back to the number on the syringe barrel that matches your dose. Check again for air bubbles. The air in the syringe will not hurt you, but too large an air bubble can reduce your dose of Nivestym. If there are still air bubbles, repeat the steps above to remove them.

J Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your healthcare provider. Do not remove the needle from the vial. Lay the vial down on its side with the needle still in the vial.

Step 6: Select and Prepare the Injection Site

K Choose the injection site**:**

- Thigh
- Stomach area (abdomen), except for a 2-inch area right around your navel (belly button)
- Upper outer area of your buttocks (only if someone else is giving you the injection)
- Outer area of upper arm (only if someone else is giving you the injection)



L Prepare and clean your injection site.

Administering the Nivestym vial

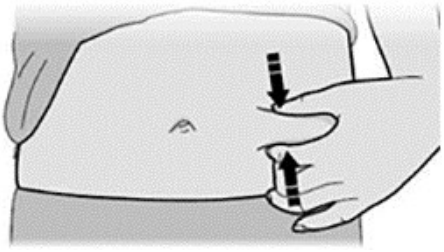
Step 7: Clean your injection site with a clean alcohol wipe.

- Let your skin dry.
- **Do not** touch this area again before injecting.
- If you want to use the same injection site, make sure it is not the same spot on the injection site area you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

Step 8: Subcutaneous (under the skin) injection

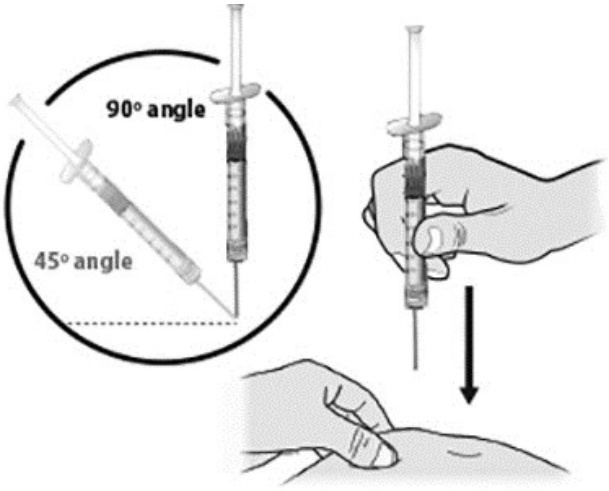
- Remove the prepared syringe and needle from the vial.

- Pinch your injection site to create a firm surface.

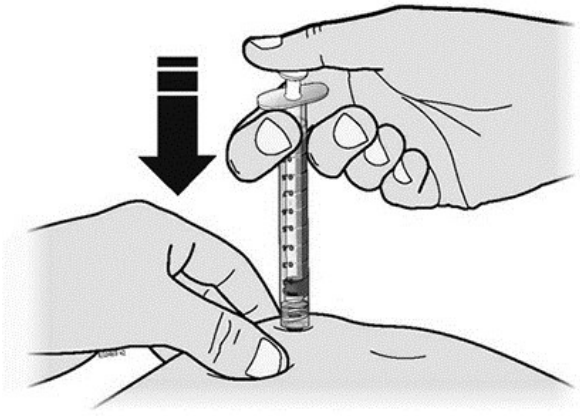


Important: Keep skin pinched while injecting.

- Hold the pinch. Insert the needle into the skin at a 45 to 90 degree angle.



- Using slow and constant pressure, push the plunger until it reaches the bottom.



- When done gently pull the syringe out of the injection site at the same 45 to 90 degree angle used to insert it.

How should I dispose (throw away) used Nivestym vial?

Step 9: Finish

- Discard (throw away) the used needle, syringe, and vial.

- Put your used syringes, needles, and vials in a sharps disposal container right away after use. **Do not throw away (dispose of)** needles, syringes and vials in your household trash.

- **If you do not have an sharps disposal container, you may use a household container that:**
  - is made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - is upright and stable during use,
  - is leak-resistant, and
  - is properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be special or local laws for disposal of used syringes and needles.

Important: Always keep the sharps disposal container out of the reach of children.

- Examine the injection site.

  If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

This Instructions for Use was prepared by:
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Last Revised: