

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr NYVEPRIA™
pegfilgrastim injection
Sterile Solution

6 mg in 0.6 mL solution (10 mg/mL) in pre-filled syringes for subcutaneous injection

Professed Standard

Immunostimulants/ Colony Stimulating Factors

ATC Code: L03AA02

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RECENT MAJOR LABEL CHANGES

8 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis	08/2021
8 WARNINGS AND PRECAUTIONS, Hematologic	08/2021

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Sections or subsections that are not applicable at the time of authorization are not listed .

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Nyvepria (pegfilgrastim) is a biosimilar biologic drug (biosimilar) to Neulasta®.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Nyvepria (pegfilgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs.

Indications have been granted on the basis of similarity between Nyvepria and the reference biologic drug Neulasta (pegfilgrastim).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

2 CONTRAINDICATIONS

Nyvepria (pegfilgrastim) is contraindicated in patients with known hypersensitivity to *E. coli*-derived products, pegfilgrastim, filgrastim, or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the **6 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 pegfilgrastim and its parent compound, filgrastim (see **7 WARNINGS AND PRECAUTIONS: General**).
- Severe sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim (see **7 WARNINGS AND PRECAUTIONS: Hematologic**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Nyvepria (pegfilgrastim) should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy (see **7 WARNINGS AND PRECAUTIONS**).

Renal impairment, including end-stage renal disease, appears to have no effect on the pharmacokinetics of pegfilgrastim and no dosage adjustment is required.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of Nyvepria is a single subcutaneous injection of 6 mg, administered once per cycle of chemotherapy. Nyvepria should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy (see **7 WARNINGS AND PRECAUTIONS**).

Health Canada has not authorized an indication for pediatric use (see **1.1 Pediatrics**).

4.4 Administration

Nyvepria is intended for subcutaneous injection only and should not be given by any other route of administration. Nyvepria should not be mixed with any diluents.

Nyvepria should not be vigorously shaken.

Nyvepria is supplied in prefilled syringes with a BD UltraSafe Plus™ Passive Needle Guard. Following administration of Nyvepria 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.

4.5 Missed Dose

If a scheduled dose is missed, Nyvepria should not be administered less than 14 days before subsequent administration of cytotoxic chemotherapy.

5 OVERDOSAGE

The maximum tolerated dose of Nyvepria (pegfilgrastim) has not been determined in humans. Pegfilgrastim administered at a dose of 300 mcg/kg (n = 12), approximately 3 times the recommended dose, exhibited an adverse event profile similar to that observed at the recommended dose.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Sterile Solution for Injection 6 mg (10 mg/mL)	Polysorbate 20 Sodium acetate Sorbitol Water for Injection

Nyvepria (pegfilgrastim) is supplied in 6 mg / 0.6 mL single-use, preservative-free, prefilled syringe (PFS) with a 27-gauge ½ inch needle and a BD UltraSafe Plus™ Passive Needle Guard for manual subcutaneous injection. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe.

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

Nyvepria is provided in a carton containing one PFS and a package insert.

Description

Nyvepria (pegfilgrastim) is a biosimilar to Neulasta. It is a long-acting form of recombinant methionyl human granulocyte-colony stimulating factor (r-metHuG-CSF), referred to as filgrastim. Nyvepria is composed of filgrastim with a 20 kDa monomethoxypolyethylene glycol propionaldehyde (mPEG-p) molecule covalently bound to the N-terminal methionine residue. Filgrastim is expressed in *Escherichia coli* (*E. coli*) as a 175 amino acid protein with a theoretical average weight of 18,799 Da; Nyvepria exhibits molecular weight dispersity with an observed distribution of approximately 37.0 to 42.5 kDa.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

Nyvepria (pegfilgrastim) has not been evaluated for PBPC (peripheral blood progenitor cell) mobilization. Therefore, it should not be used in that setting.

Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of pegfilgrastim and its parent compound, filgrastim. Patients receiving Nyvepria who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Simultaneous Use with Chemotherapy and Radiation Therapy

The safety and efficacy of Nyvepria administered concurrently with cytotoxic chemotherapy have not been established. Because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Nyvepria should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see **4 DOSAGE AND ADMINISTRATION**).

The safety and efficacy of Nyvepria have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (e.g., nitrosoureas), mitomycin C, or myelosuppressive doses of anti-metabolites such as 5-fluorouracil (5-FU). Concomitant use of Nyvepria with 5-FU or other anti-metabolites has not been evaluated in humans, although pegfilgrastim has been studied and shown to potentiate myelosuppression in animal models (see **16 NONCLINICAL TOXICOLOGY**).

The safety and efficacy of Nyvepria have not been evaluated in patients receiving radiation therapy, except for patients with breast or lung cancer.

Carcinogenesis and Mutagenesis

No carcinogenesis or mutagenesis studies were conducted with Nyvepria.

Potential Effect on Malignant Cells

Nyvepria (pegfilgrastim) and filgrastim are growth factors that primarily stimulate production of

neutrophils and neutrophil precursors by binding to the G-CSF receptor. Overall, the possibility that Nyvepria can act as a growth factor for any tumour type cannot be excluded. The use of Nyvepria in chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS) has not been studied.

MDS and AML in Breast and Lung Cancer Patients

In the post-marketing observational study setting, findings showed that pegfilgrastim is associated with an increased risk of MDS and AML in breast and lung cancer patients when used in conjunction with chemotherapy and/or radiotherapy. Monitor patients for signs and symptoms of MDS/AML in these settings.

Cardiovascular

Aortitis

Aortitis has been reported in patients receiving pegfilgrastim 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 pegfilgrastim or filgrastim. 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

Sickle Cell Crises

Severe sickle cell crises have been associated with the use of pegfilgrastim sterile solution for injection in patients with sickle cell trait or sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell trait and sickle cell disease should prescribe Nyvepria for such patients, and only after careful consideration of the potential risks and benefits.

Leukocytosis

In clinical studies with pegfilgrastim, white blood cell counts of $100 \times 10^9/L$ or greater have been reported in less than 1% of patients with cancer receiving myelosuppressive chemotherapy ($n = 930$), and were not associated with any reported adverse clinical effects (see **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

In studies of pegfilgrastim administration after chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see **8 ADVERSE REACTIONS**). Because of the potential for patients to receive full doses of chemotherapy on the prescribed schedule, patients may be at greater risk of thrombocytopenia, anemia, and non-hematologic consequences of increased chemotherapy doses (please refer to the prescribing information for specific chemotherapy agents). Regular monitoring of hematocrit value and platelet count is recommended. Furthermore, care should be exercised in the administration of Nyvepria in conjunction with drugs known to lower platelet count.

Thrombocytopenia

Thrombocytopenia, including serious events, has been reported in patients receiving pegfilgrastim. Platelet counts should be monitored regularly as clinically indicated.

Immune

Hypersensitivity/Allergic Reactions

Hypersensitivity including serious allergic reactions and anaphylactic reactions, skin rash, urticaria and erythema/flushing occurring on initial or subsequent treatment have been reported both with pegfilgrastim and filgrastim. In some cases, symptoms have recurred with re-challenge, suggesting a causal relationship. In rare cases, allergic reactions, including anaphylactic reactions, recurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered and further use of Nyvepria should be discontinued. Antibodies to filgrastim or pegfilgrastim have been reported, although no neutralizing antibodies have been reported (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings; Immunogenicity**). Do not administer filgrastim to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Cutaneous Vasculitis

Uncommon ($\geq 1/1,000$ to $< 1/100$) events of cutaneous vasculitis have been reported in patients treated with pegfilgrastim sterile solution for injection. The mechanism of vasculitis in patients receiving pegfilgrastim is unknown.

Monitoring and Laboratory Tests

To assess a patient's hematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count (CBC) and platelet count should be obtained before chemotherapy is administered. Pegfilgrastim produced ANC (absolute neutrophil count) profiles similar to daily filgrastim, including earlier ANC nadir, shorter duration of severe neutropenia, and accelerated ANC recovery, compared with ANC profiles observed without growth factor support. Regular monitoring of hematocrit value, white blood cell count and platelet count, as clinically indicated, is recommended.

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.

Reproductive Health: Female and Male Potential

- **Fertility**

No studies evaluating reproduction in humans were conducted with Nyvepria.

- **Function**

No studies evaluating sexual function in humans were conducted with Nyvepria.

Respiratory

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) has been reported following administration of pegfilgrastim

and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Nyvepria who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Nyvepria should be discontinued and/or withheld until resolution of ARDS, and patients should receive appropriate medical management for this condition.

7.1 Special Populations

7.1.1 Pregnant Women

There were no pregnant women exposed to pegfilgrastim in clinical trials. Nyvepria should be used during pregnancy only if the potential benefit outweighs the risk to the fetus (see **16 NONCLINICAL TOXICOLOGY**).

7.1.2 Breast-feeding

It is not known whether pegfilgrastim is excreted in human milk. Because many drugs are excreted in human milk, Nyvepria is not recommended for women who are breast-feeding. Nyvepria should only be administered to a nursing woman if the potential benefit outweighs the risk.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Of the total number of patients with cancer who received pegfilgrastim in clinical studies (n = 930), 139 patients (15%) were 65 years or older and 18 patients (2%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients; however, due to the small number of elderly subjects, small but clinically relevant differences cannot be excluded.

8 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Nyvepria (pegfilgrastim) 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.

8.1 Adverse Reaction Overview

The most frequently reported study drug-related adverse event was bone pain, for which the incidence in patients treated with pegfilgrastim was similar to that in patients treated with filgrastim. Bone pain was generally reported as mild-to-moderate, could be controlled in most patients with non-narcotic analgesia.

See **7 WARNINGS AND PRECAUTIONS** regarding Splenic Rupture, ARDS, Hypersensitivity/Allergic Reactions, and Sickle Cell Crises.

8.2 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.

Safety data are based on 7 randomized clinical trials involving 932 patients with lymphoma and solid tumours (breast and thoracic) who received pegfilgrastim after non-myeloablative cytotoxic chemotherapy. Common adverse events occurred at similar rates between the treatment arms in both the filgrastim-controlled trials (pegfilgrastim, n = 465; filgrastim, n = 331) and the placebo-controlled trial (pegfilgrastim, n = 467; placebo, n = 461). Most adverse experiences were attributed by the investigator as the sequelae of the underlying malignancy or cytotoxic chemotherapy. In the filgrastim-controlled trials, these adverse experiences occurred at rates between 15% and 72% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. A summary of the most frequently reported adverse reactions in these randomized clinical trials can be found in Table 2 and Table 3.

In clinical trials comparing pegfilgrastim to filgrastim, medullary bone pain was reported in 26% of pegfilgrastim-treated patients, which was comparable to the incidence in filgrastim-treated patients. In the study comparing pegfilgrastim to placebo, the incidence of bone pain was 23% vs. 16%, respectively. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 17% (for all bone pain type AEs; 10% for specifically “bone pain”) of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain. No patient withdrew from study due to bone pain.

Across all studies, no life-threatening or fatal adverse events were attributed to pegfilgrastim. There was only one serious adverse event (dyspnea) reported as possibly related to pegfilgrastim in a single patient. No events of pleuritis, pericarditis, or other major systemic reactions to pegfilgrastim were reported.

No clinically significant changes in vital signs were observed. No evidence of interaction of pegfilgrastim with other drugs was observed in the course of clinical trials (see **7 WARNINGS AND PRECAUTIONS**).

Table 2: Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Filgrastim as Comparator

Body System and Preferred Term	Pegfilgrastim (n = 465)	Filgrastim (n = 331)
Application Site		
Injection Site Pain	16 (3%)	9 (3%)
Body as a whole		
Pain	8 (2%)	4 (1%)

Chest Pain (Non-Cardiac)	4 (1%)	3 (1%)
Edema Periorbital	3 (1%)	0 (0%)
Fever	3 (1%)	4 (1%)
CNS/PNS		
Headache	20 (4%)	12 (4%)
Musculoskeletal		
Skeletal Pain	96 (21%)	89 (27%)
Myalgia	32 (7%)	25 (8%)
Arthralgia	27 (6%)	19 (6%)
Back Pain	19 (4%)	26 (8%)
Limb Pain	12 (3%)	7 (2%)
Musculo-Skeletal Pain	5 (1%)	4 (1%)
Neck Pain	4 (1%)	3 (1%)

* Most frequently reported events were considered to be those events reported in $\geq 1\%$ of the patients in the pegfilgrastim group.

Table 3: Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Placebo Control

Body System and Preferred Term	Pegfilgrastim (n = 467)	Placebo (n = 461)
Blood and Lymphatic System Disorders		
Leukocytosis	5 (1%)	1 (0%)
Gastrointestinal Disorders		
Diarrhea	9 (2%)	10 (2%)
General Disorders and Administration Site Conditions		
Pyrexia	8 (2%)	9 (2%)
Fatigue	3 (1%)	5 (1%)
Infections and Infestations		
Influenza	6 (1%)	5 (1%)
Musculoskeletal and Connective Tissue Disorders		
Bone Pain	62 (13%)	41 (9%)
Myalgia	26 (6%)	23 (5%)
Arthralgia	32 (7%)	19 (4%)
Polymyalgia	8 (2%)	7 (2%)

Musculoskeletal Pain	14 (3%)	5 (1%)
Pain in Limb	11 (2%)	5 (1%)
Back Pain	8 (2%)	4 (1%)
Polyarthralgia	5 (1%)	0 (0%)
Nervous System Disorders		
Headache	6 (1%)	2 (0%)
Skin and Subcutaneous Tissue Disorders		
Alopecia	8 (2%)	9 (2%)

* Most frequently reported events were considered to be those events reported in $\geq 1\%$ of the patients in the pegfilgrastim group.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Health Canada has not authorized an indication for pediatric use for Nyvepria (see **1.1 Pediatrics**). The safety and efficacy of the reference product have not been established and therefore is not indicated for use in pediatric patients (< 18 years of age).

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse drug reactions were reported at an incidence of <1% in controlled clinical studies (occurring in more than 1 patient, with higher frequency than filgrastim):

General Disorders and Administration Site Conditions: injection site bruising.

Infections and Infestations: rhinitis.

Nervous System Disorders: hypertonia.

Skin and Subcutaneous Tissue Disorders: periorbital edema.

The following adverse drug reactions were reported at an incidence of <1% in controlled clinical studies (occurring in more than 1 patient, with higher frequency than placebo):

General Disorders and Administration Site Conditions: chest pain, pain.

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

Spontaneously reversible elevations in LDH, alkaline phosphatase, and uric acid of mild-to-moderate severity were observed. Most changes have been attributed to post-cytokine bone marrow expansion as well as to chemotherapy and metastatic disease. The incidences of these changes, presented for pegfilgrastim versus filgrastim and placebo, were: LDH (18% versus 29% and 18%), alkaline phosphatase (11% versus 16% and 12%), and uric acid [10% versus 9% and 13% (1% of uric acid reported cases for filgrastim and pegfilgrastim treatment groups were classified as severe)].

In clinical studies with pegfilgrastim, white blood cell counts of $100 \times 10^9/L$ or greater have been reported in less than 1% of patients with cancer receiving myelosuppressive chemotherapy (n = 930), and were not associated with any reported adverse clinical effects.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving pegfilgrastim has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim or pegfilgrastim, the nature and specificity of these antibodies have not been adequately studied. No neutralizing antibodies have been detected using a cell-based bioassay in 46 (9%, n =534) patients who apparently developed binding antibodies. 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 sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to pegfilgrastim 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 pegfilgrastim may cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

For detailed immunogenicity information for Nyvepria, see **14.4 Immunogenicity**.

8.5 Post-Market Adverse Reactions

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

- Splenomegaly (enlarged spleen) and Splenic rupture (see **7 WARNINGS AND PRECAUTIONS, General, Splenic Rupture**)
- Acute respiratory distress syndrome (ARDS) (see **7 WARNINGS AND PRECAUTIONS, Respiratory**)
- Allergic reactions (see **7 WARNINGS AND PRECAUTIONS: Immune, Hypersensitivity/Allergic Reactions**)
- Sickle cell crisis (see **7 WARNINGS AND PRECAUTIONS: Hematologic**)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML) in Breast and Lung Cancer Patients (see **7 WARNINGS AND PRECAUTIONS, Hematologic**)
- Injection site reactions (pain, induration, and local erythema)
- Generalized erythema and flushing
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Cutaneous Vasculitis (see **7 WARNINGS AND PRECAUTIONS, Immune**)
- Capillary Leak Syndrome (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**)
- Glomerulonephritis (see **7 WARNINGS AND PRECAUTIONS, Renal**)
- Aortitis (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drug interactions between pegfilgrastim and other drugs have not been studied. Drugs such as lithium

that may potentiate the release of neutrophils should be used with caution; such patients should have more frequent monitoring of their neutrophil counts.

9.3 Drug-Behavioural Interactions

No drug-behavioural interactions have been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Both pegfilgrastim and filgrastim are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared to filgrastim.

10.2 Pharmacodynamics

See information in 10.3 below.

10.3 Pharmacokinetics

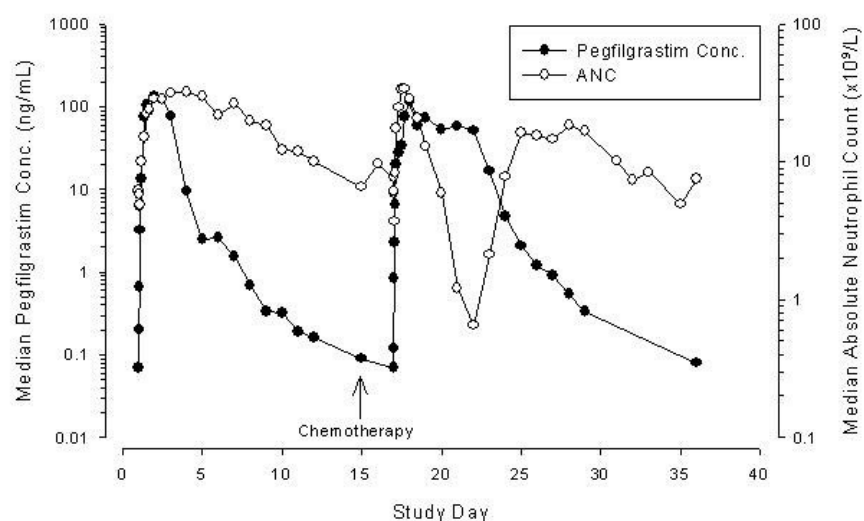
The pharmacokinetics and pharmacodynamics of pegfilgrastim were studied in patients with cancer. The pharmacokinetics of pegfilgrastim were nonlinear in cancer patients and clearance decreased with increases in dose. Neutrophil-mediated clearance is an important component of the clearance of pegfilgrastim, and serum clearance is related to the number of neutrophils (neutrophil-mediated, self-regulating clearance). Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declined rapidly at the onset of neutrophil recovery, following myelosuppressive chemotherapy (see Figure 1). In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed in cancer patients. The half-life of pegfilgrastim ranged from 25 to 49 hours after SC injection.

Table 4: Summary of Pharmacokinetic Parameters of Pegfilgrastim in Cancer Patients After SC Administration

	C_{max}	t_½	AUC_{0-∞}	Clearance
Single dose*	78.3-175	25-49 hr	5640-15000	6.68-17.7
Median	ng/mL		ng·hr/mL	mL/hr/kg

* Doses of 100 mcg/kg and 6 mg

Figure 1. Median Pegfilgrastim Serum Concentration and Absolute Neutrophil Count Profiles in Patients with Non-Small Cell Lung Cancer (n = 3) After a Single Injection of Pegfilgrastim 100 mcg/kg Administered Before and After Chemotherapy



Special Populations and Conditions

- **Pediatrics:** The pharmacokinetic profile in pediatric populations has not been assessed.
- **Geriatrics:** no differences were observed in the pharmacokinetics of geriatric patients with cancer (≥ 65 years of age) compared to younger patients (< 65 years of age) (see **7.1.4 Geriatrics**).
- **Sex:** no gender-related differences were observed in the pharmacokinetics of pegfilgrastim.
- **Ethnic Origin:** The effect of race on pharmacokinetics has not been adequately assessed.
- **Hepatic Insufficiency:** The pharmacokinetic profile in patients with hepatic insufficiency has not been assessed.

- **Renal Insufficiency:** Renal impairment, including end-stage renal disease, appears to have no effects on the pharmacokinetics of pegfilgrastim.

11 STORAGE, STABILITY AND DISPOSAL

Nyvepria (pegfilgrastim) should be stored in the refrigerator at 2°C to 8°C. Do not store in the freezer. Store in the 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 Nyvepria if frozen more than once.

Nyvepria may be allowed to reach room temperature for a maximum of 15 days. Any prefilled syringe 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. Nyvepria should not be administered if discoloration or particulates are observed.

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

12 SPECIAL HANDLING INSTRUCTIONS

Nyvepria (pegfilgrastim) should not be vigorously shaken.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	pegfilgrastim
Chemical name:	pegylated recombinant methionyl human granulocyte- colony stimulating factor
Molecular formula and molecular mass:	Nyvepria pegfilgrastim exhibits molecular weight dispersity with an observed distribution of approximately 37.0 to 42.5 kDa.
Structural formula:	<p>Pegfilgrastim is composed of filgrastim (recombinant methionyl human G-CSF) with a 20,000 dalton monomethoxypolyethylene glycol propionaldehyde (mPEG-p) molecule covalently bound to the N-terminal methionine residue. Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by <i>Escherichia coli</i> (<i>E. coli</i>) bacteria into which the human G-CSF gene has been inserted. Filgrastim has an amino acid sequence that is identical to the natural sequence predicted by human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in <i>E. coli</i>. Because filgrastim is produced in <i>E. coli</i>, the protein is nonglycosylated and thus differs from G-CSF isolated from a human cell.</p>
Physicochemical properties:	pH 3.8 – 4.3

Product Characteristics:

Nyvepria (pegfilgrastim injection) is a sterile, clear, colourless liquid.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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

- An open-label, randomized, single-dose, comparator-controlled, crossover pharmacodynamic (PD)/pharmacokinetic (PK) study in healthy volunteers (ZIN-130-1505 [C1221001], hereafter referred to as ZIN-130-1505).
- A randomized, open-label, two-dose, non-inferiority, parallel-group immunogenicity study in healthy volunteers (C1221005).

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in Table 5.

Table 5: Summary of Trial Design and Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ZIN-130-1505	An open-label, randomized, single-dose, comparator-controlled, 3-treatment, 3-period, 6-sequence, crossover study to assess the PD and PK of Nyvepria, US-Neulasta and EU-Neulasta in healthy volunteers	Subjects received 1 of the following study drugs: Nyvepria or; US-Neulasta or; EU-Neulasta in each of the 3 treatment periods as a single 6 mg SC injection in the deltoid region on Study Day 1 in each treatment period. There was at least 56 days of washout between each treatment.	Randomized: 153 subjects (153 dosed) Treatments: N = 148 subjects received at least 1 dose of 6 mg Nyvepria N = 146 subjects received at least 1 dose of 6 mg US-Neulasta N = 148 subjects received at least 1 dose of 6 mg EU-Neulasta	30.4 years (18-65)	Female: 72 (47.1%) Male: 81 (52.9%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
C1221005	A randomized, open-label, parallel design non-inferiority study to assess the immunogenicity of two 6 mg SC doses of Nyvepria and US-Neulasta in healthy volunteers	Subjects received 2 doses of the following study drugs: Nyvepria or US-Neulasta as a 6 mg SC injection in the deltoid region. The period between the 2 doses was approximately 1 month.	Randomized: 422 subjects (420 dosed) Treatments: N = 210 subjects received at least 1 dose of 6 mg Nyvepria N = 210 subjects received at least 1 dose of 6 mg US-Neulasta	36.61 years (18-65)	Female: 237 (56.4%) Male: 183 (43.6%)
PD = pharmacodynamic; PK = pharmacokinetic; US = United States; EU = European Union; SC = subcutaneous					

14.2 Study Results

See 14.3 Comparative Bioavailability Studies.

14.3 Comparative Bioavailability Studies

Pharmacodynamic and pharmacokinetic comparability of Nyvepria and Neulasta were evaluated in Study ZIN-130-1505, a single centre, randomised, open label, single dose, comparator controlled, 3 treatment, 3 period, 6 sequence, crossover study that compared Nyvepria to US-Neulasta and EU-Neulasta following subcutaneous (SC) administration in 153 healthy subjects.

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

Table 6: Study ZIN-130-1505 – Analysis of Primary Pharmacokinetic Parameters

Pegfilgrastim (1 x 6 mg) From measured data				
Geometric Mean Arithmetic Mean (CV %)				
Parameter	Nyvepria¹ N = 142	EU-Neulasta² N = 142	% Ratio of Geometric Means	90% Confidence Interval³
AUC _T (h•pg/mL)	5341685.8 6720232.1 (72.6)	5473417.1 6829675.9 (70.5)	97	(91, 105)
AUC _{0-inf} (h•pg/mL)	5359890.1 6734344.6 (72.5)	5493479.4 6845090.4 (70.3)	97	(91, 105)
C _{MAX} (pg/mL)	152927.4 187290.8 (60.3)	160688.0 193412.0 (58.6)	95	(88, 102)
T _{MAX} ⁴ (h)	16.0 (8.0-48.0)	16.0 (10.0-48.0)	Not applicable	Not applicable
T _½ ⁵ (h)	49.4 (13.6)	54.5 (23.6)	Not applicable	Not applicable
<p>1. Nyvepria (pegfilgrastim) by Pfizer. 2. EU-Neulasta (EU-authorized Neulasta[®] (pegfilgrastim)) by Amgen Inc. 3. Acceptance Interval was 80.0% to 125.0%. 4. Expressed as the median (range). 5. Expressed as the arithmetic mean (SD).</p> <p>CV = coefficient of variation AUC_T = area under the serum pegylated filgrastim concentration curve from time zero to the last measurable time point AUC_{0-inf} = area under the serum pegylated filgrastim concentration curve from time zero to infinity C_{max} = maximum observed serum pegylated filgrastim concentration T_{max} = time to maximum observed serum pegylated filgrastim concentration T_½ = elimination half-life SD = standard deviation</p> <p>Results presented are based upon the safety population who received all 3 treatments (Nyvepria, US-Neulasta, and EU-Neulasta). One subject who was considered an outlier was excluded from the analysis.</p>				

Study ZIN-130-1505 (single dose study in healthy volunteers)

The results of the pharmacodynamics comparisons are shown in **Table 7**.

Table 7: Study ZIN-130-1505 – Analysis of Primary Pharmacodynamic Parameters

Pegfilgrastim (1 x 6 mg) From measured data				
Geometric Mean Arithmetic Mean (CV %)				
Parameter	Nyvepria¹ N = 142	EU-Neulasta² N = 142	% Ratio of Geometric Means	95% Confidence Interval³
AUEC _{ANC} (h×10 ⁹ /L)	4537.7 4680.3 (25.1)	4615.2 4748.9 (23.9)	98	(96, 100)
ANC_C _{max} (×10 ⁹ /L)	30.3 31.5 (28.4)	30.6 31.8 (26.9)	99	(96, 101)
1. Nyvepria (pegfilgrastim) by Pfizer. 2. EU-Neulasta (EU-authorized Neulasta [®] (pegfilgrastim)) by Amgen Inc. 3. Acceptance Interval was 80.0% to 125.0% CV = coefficient of variation AUEC _{ANC} = area under the effect ANC-time curve from time zero to the last measurable time point ANC_C _{max} = maximum effect ANC = absolute neutrophil count Results presented are based upon the safety population who received all 3 treatments (Nyvepria, US-Neulasta, and EU-Neulasta). One subject who was considered an outlier was excluded from the analysis.				

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

14.4 Immunogenicity

A tiered approach was used for anti-drug (anti-pegfilgrastim and anti-polyethylene glycol [anti-PEG]) antibody (ADA) testing. Immunogenicity was assessed using a validated electrochemiluminescence (ECL) assay against pegfilgrastim. A separate validated ELISA assay was used to detect antibodies to the polyethylene glycol (PEG) moiety. A cell-based assay was used to detect neutralizing antibodies (NABs).

ZIN-130-1505 (Single dose study in healthy volunteers)

In Study ZIN-130-1505, anti-drug (anti-pegfilgrastim and anti-PEG) antibodies were assessed from blood samples collected prior to dose on Day 1, on Day 13 of each period, and at the Day 30 follow-up visit of each treatment period. Ten (10) subjects confirmed positive post-baseline for anti-pegfilgrastim antibody at least once during the study: 6 subjects receiving Nyvepria (4.1%), 2 subjects (1.4%) receiving US-Neulasta, and 2 subjects (1.4%) receiving EU-Neulasta. The incidence of anti-PEG antibody was comparable in all treatment arms.

Two (2) of the 10 anti-pegfilgrastim antibody positive subjects, both receiving Nyvepria, had a single sample positive for NAb that occurred on Period 1 Day 13.

C1221005 (Non-inferiority Immunogenicity study in healthy volunteers)

In Study C1221005, anti-drug (anti-pegfilgrastim and anti-PEG) antibodies were assessed from blood samples collected on Day 1 (pre-treatment baseline), Day 13, and Day 30 (±2) in Treatment Period 1; and on Day 13, Day 30 (±2) (or Early Withdrawal) and Day 60 (±5) in Treatment Period 2. Of the 420 subjects who were randomized and received at least 1 dose of study drug, a total of 32 subjects had a confirmed positive anti-pegfilgrastim antibody result, at least once during the study (14 subjects [6.7%] in the Nyvepria group and 18 subjects [8.6%] in the US-Neulasta group). Non-inferiority was established, as the upper limit of the 95% CI for the risk difference (-1.91% [95% CI: -7.36%, 3.36%]) was ≤ 10%. The incidence of anti-PEG antibody was comparable in both treatment arms.

There was no evidence of NAb among subjects in either treatment group who had negative anti-pegfilgrastim antibody result at baseline. There was 1 subject with confirmed positive baseline anti-pegfilgrastim antibody who received Nyvepria and who had 2 anti-pegfilgrastim antibody samples tested positive for NAb.

14.5 Clinical Trials - Reference Biologic Drug

Study demographics and trial design

Table 8: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
980226	Phase 3, double-blind, randomized, filgrastim controlled	Single SC dose of 100 mcg/kg/day pegfilgrastim or daily SC dose of 5 mcg /kg/day filgrastim, up to 4 cycles	310 (154 pegfilgrastim, 156 filgrastim)	50.9 (25-81) pegfilgrastim 51.8 (26-87) filgrastim	306 females, 4 males
990749	Phase 3, double-blind, randomized, filgrastim controlled	6 mg single dose of pegfilgrastim SC or 5 mcg /kg/day filgrastim up to 14 days, up to 4 cycles	157 (80 pegfilgrastim, 77 filgrastim)	51.9 (31-75) pegfilgrastim 52.6 (30-74) filgrastim	156 females, 1 male

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
20010144	Phase 3, double-blind, placebo-controlled, randomized	Pegfilgrastim, 6 mg SC, single dose every 3 weeks, up to 12 weeks	928 (463 pegfilgrastim, 465 placebo)	51.9 (21-88) pegfilgrastim 52.1 (24-76) placebo	99% female

Study Results

Clinical Experience: Response to pegfilgrastim

Pegfilgrastim administered as a single SC injection, after each cycle of chemotherapy, has been shown to be safe and effective in reducing neutropenia and associated clinical sequelae in a variety of chemotherapy settings.

Pegfilgrastim has been evaluated in three Phase 3, randomized, double-blind, controlled studies. Results from two active controlled studies (n = 467) conducted in patients with breast cancer undergoing up to 4 cycles of chemotherapy with doxorubicin and docetaxel demonstrated non-inferiority of pegfilgrastim to filgrastim. A clinically and statistically similar reduction in the duration of severe neutropenia (absolute neutrophil count [ANC] < 0.5 x 10⁹/L; WHO grade 4) was seen in patients who received a single injection of pegfilgrastim, either 6 mg fixed dose or 100 mcg/kg, compared with patients who received a mean of 11 daily injections (cycle 1) of filgrastim 5 mcg/kg/day.

The mean (std dev) duration of severe neutropenia in cycle 1 in patients who received a single fixed-dose (6 mg) SC injection of pegfilgrastim (n = 68) was 1.8 (1.4) days compared with 1.6 (1.1) days in patients who received daily injections (range: 7-14 injections) of filgrastim (n = 62). The difference in means was 0.18 days (95% CI of -0.23 to 0.61). Durations of severe neutropenia were also comparable between treatment groups in all subsequent cycles. The rate of febrile neutropenia (temperature ≥ 38.2°C with an ANC < 0.5 x 10⁹/L) across all cycles was lower for patients receiving pegfilgrastim (13%) compared to patients receiving filgrastim (20%) (-7% difference; 95% CI of -19% to +5%). A single SC injection of pegfilgrastim per chemotherapy cycle was safe and well tolerated (see **8 ADVERSE REACTIONS**).

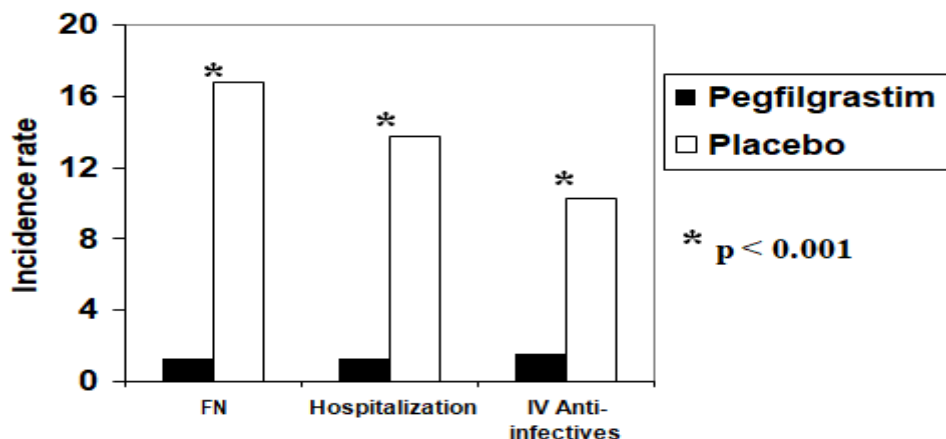
The third study employed a placebo control and evaluated the effect of pegfilgrastim on the incidence of febrile neutropenia when administered in first and all subsequent cycles of a moderately myelosuppressive chemotherapy regimen, docetaxel administered at 100 mg/m² Q3W for 4 cycles, which has been reported to be associated with a febrile neutropenia rate of 10% to 20%.

In this study, 928 patients with metastatic or non-metastatic breast cancer were treated with docetaxel. On day 2 of cycle 1, patients were randomized to receive either a single SC dose of 6 mg of pegfilgrastim or placebo. Patients who received pegfilgrastim in cycle 1 were scheduled to receive pegfilgrastim in all subsequent cycles. Patients who received placebo in cycle 1 were scheduled to receive placebo in all subsequent cycles; however, patients who experienced febrile neutropenia would receive open-label pegfilgrastim.

The incidence of febrile neutropenia was statistically significantly lower for patients randomized to receive pegfilgrastim versus placebo (1% versus 17%, p ≤ 0.001). The incidence of hospitalizations

and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia were significantly lower in the pegfilgrastim group compared with placebo [1% versus 14%, $p \leq 0.001$; and 2% versus 10%, $p \leq 0.001$, respectively (see Figure 2)].

Figure 2. Percentage of Subjects with Febrile Neutropenia (FN), Who Were Hospitalized, and Who Received IV Anti-infectives for FN



Data from Phase 2 studies in patients with various malignancies undergoing a variety of chemotherapy regimens further support the safety and efficacy of pegfilgrastim. Dose-finding studies in patients with breast cancer ($n = 152$), thoracic tumours ($n = 92$), and non-Hodgkin's lymphoma (NHL) ($n = 49$) demonstrated that the efficacy of a single injection of pegfilgrastim 100 mcg/kg was similar to daily injections of filgrastim 5 mcg/kg/day, and superior to pegfilgrastim doses of 30 or 60 mcg/kg, at reducing the duration of severe neutropenia and the rate of febrile neutropenia. A randomized Phase 2 study of patients with NHL or Hodgkin's lymphoma ($n = 60$) further supports the safety and efficacy of pegfilgrastim.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The preclinical toxicology of pegfilgrastim was studied in Sprague-Dawley® rats and cynomolgus monkeys. A single-dose IV study was conducted in rats. Pegfilgrastim caused no clinical signs or mortality at single IV doses up to 10,000 mcg/kg in rats.

Repeat-dose studies included 2-week SC (every-other-day dosing) and 6-month SC/IV (weekly dosing) studies in rats and a 1-month SC (weekly dosing) study in monkeys. Dosing was intermittent to mimic intended human use of pegfilgrastim. Pegfilgrastim was well tolerated for 6 months at once-weekly doses up to 1000 mcg/kg SC or 300 mcg/kg IV in rats, and for 1 month at once-weekly doses up to 750

mcg/kg SC in cynomolgus monkeys. No effects on body weight, food consumption, or survival were observed. Pegfilgrastim caused an increase in leukocyte counts, primarily segmented neutrophils, but also some increases in band neutrophils, monocytes, and lymphocytes. Pegfilgrastim also modestly decreased erythrocyte counts, hemoglobin and hematocrit levels, decreased serum cholesterol, slightly decreased serum potassium, and increased serum alkaline phosphatase. Splenomegaly was the principal gross pathological finding. Histopathological examination revealed increased neutrophilic granulopoiesis in bone marrow and extramedullary hematopoiesis in spleen, liver, and/or lymph nodes. Leukocytosis in spleen, liver, and lymph nodes, and mild inflammation and mononuclear cell infiltrate at the injection site were additionally observed in monkeys treated with pegfilgrastim. Observed changes tended to reverse upon cessation of treatment. Changes specific to every-other-day dosing in rats (≥ 500 mcg/kg only) included slightly increased serum ALT and/or AST, mild myelofibrosis in bone marrow, and increased osteoblastic/osteoclastic activity in bone. Little or no seroreactivity to pegfilgrastim was evident in rats, whereas a dose- and time-dependent increase in seroreactivity was observed in monkeys; however, pegfilgrastim-induced neutrophil increases were maintained.

Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when given every-other-day at doses as low as 50 mcg/kg. Nonclinical data in pregnant rats indicate that very low levels of pegfilgrastim may cross the placenta.

Pegfilgrastim administered SC to pregnant rabbits at doses of 200 and 250 mcg/kg every-other-day during the period of organogenesis was associated with an increased incidence of abortions.

Increased postimplantation loss due to early resorptions and decreased numbers of live fetuses were observed at pegfilgrastim doses of 200 to 1000 mcg/kg every other day. Decreased maternal food consumption and/or weight gain and decreased fetal weight were observed at doses of 50 to 1000 mcg/kg every other day. Pegfilgrastim did not cause visceral or skeletal malformations in rabbit fetuses at doses as high as 200 mcg/kg every-other-day and did not cause external malformations in rabbit fetuses at doses as high as 1000 mcg/kg every other day.

Pegfilgrastim was not associated with an increase in external, visceral, or skeletal malformations in fetuses when administered by SC injection to pregnant rats during the period of organogenesis at dose levels up to 1000 mcg/kg every other day. However, an increased incidence of wavy ribs, generally regarded as a reversible pathological finding, was observed in rat fetuses at dose levels of 300 and 1000 mcg/kg every other day. No maternal or neonatal toxicities were observed in female rats administered once-weekly SC injections of pegfilgrastim up to 1000 mcg/kg in a pre- and postnatal developmental study.

Filgrastim is known to be negative in bacterial mutagenesis assays (Ames assay). Pegfilgrastim did not cause precancerous or cancerous lesions in Sprague-Dawley[®] rats after once-weekly SC injections of up to 1000 mcg/kg for 6 months. Given the similar biochemical activity to filgrastim, the chemical nature of the PEG moiety, and extensive clinical experience with filgrastim, it is considered unlikely that pegfilgrastim would be carcinogenic when used as directed.

Pegfilgrastim is a growth factor that primarily stimulates production of neutrophils and neutrophil precursors; however, the G-CSF receptor through which pegfilgrastim and filgrastim act has been found on tumour cell lines, including some myeloid, T-lymphoid, lung, head and neck, and bladder tumour cell lines. *In vitro* proliferation has been observed in response to filgrastim in some of these cell lines, particularly acute myeloid leukemia (AML) cell lines.

Indices of mating or fertility in male and female Sprague-Dawley® rats were not adversely affected by once-weekly SC injections of pegfilgrastim of up to 1000 mcg/kg for 2 to 4 weeks before and during cohabitation.

16.1 Comparative Non-Clinical Pharmacology and Toxicology

16.1.1 Comparative Non-Clinical Pharmacodynamics

In vitro Studies

Several complementary functional assays were utilized to assess the comparability of biological activity between Nyvepria (pegfilgrastim), pegfilgrastim-US and pegfilgrastim-EU, including an in vitro cell-based proliferation assay, a competitive receptor binding assay, and a Surface Plasmon Resonance (Biacore) assay for determination of receptor binding affinity and the binding rate kinetics (Table 8). These functional assays are directly related to the pegfilgrastim therapeutic mechanism of action that involves pegfilgrastim binding to receptors on the surface of hematopoietic cells in the bone marrow followed by concentration-dependent cell proliferation and differentiation.

The results of the in vitro functional assays were comparable between Nyvepria and Neulasta.

Data from the comparative biological activities' studies met the analytical similarity acceptance criteria. The in vitro potency results demonstrate that the structural and functional properties of the pegfilgrastim protein in Nyvepria, US-Neulasta, and EU-Neulasta are similar in terms of the capability for induction of receptor-activated proliferation of hematopoietic cells. These results, together with the receptor binding (% relative potency) and receptor binding affinity and kinetics results, demonstrate that the pegfilgrastim in Nyvepria, US-Neulasta, and EU-Neulasta have similar functional activity.

16.1.2 Comparative Toxicology

A comparative 4-week rat toxicity study was conducted with once weekly subcutaneous administration of 200 or 1800 µg/kg of Nyvepria, pegfilgrastim-US or pegfilgrastim-EU. A comparable toxicological profile was demonstrated between treatment groups, and no unexpected toxicities were identified.

17 SUPPORTING PRODUCT MONOGRAPHS

Neulasta® (Sterile Solution for Injection, 10 mg/mL), Control No. 242732, Product Monograph, Amgen Canada Inc., January 8, 2021

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Nyvepria™ (pronounced **Nigh-VEP' ree-ah**)

Pegfilgrastim Injection

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

Nyvepria is a biosimilar biologic drug (biosimilar) to the reference biologic drug Neulasta[®]. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

Serious Warnings and Precautions

- Your spleen may become enlarged and can rupture while taking Nyvepria. A ruptured spleen can cause death. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area.
- If you have a sickle cell trait or sickle cell disease, make sure that you tell your doctor before you start taking Nyvepria 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 pegfilgrastim. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim.

What is Nyvepria used for?

Nyvepria is used to treat neutropenia (nu-tro-**peen**-ee-ah). Neutropenia is a condition where the body makes too few white blood cells and which may be caused by drugs used to treat cancer. Neutropenia is the most serious common side-effect of chemotherapy. Neutropenia predisposes your body to infections and prevents you from fighting them. Your doctor has decided to prescribe Nyvepria for you to increase the number of neutrophils (**nu**-tro-fils), which will fight infections.

How does Nyvepria work?

Nyvepria works by stimulating the bone marrow to make white blood cells. To make sure Nyvepria is working, your doctor may ask that you have regular blood tests to count the number of white blood cells. It is important to follow the doctor's instructions about these tests.

What are the ingredients in Nyvepria?

Medicinal ingredients: pegfilgrastim

Non-medicinal ingredients: polysorbate 20, sodium acetate, sorbitol, and water for injection

Nyvepria comes in the following dosage forms:

Prefilled syringe with a BD UltraSafe Plus™ Passive Needle Guard containing 6 mg / 0.6 mL (10 mg/mL) of pegfilgrastim.

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

Do not use Nyvepria if:

- You are allergic to pegfilgrastim (Nyvepria), filgrastim, or any of the ingredients of Nyvepria. Check the section above called, “What are the ingredients in Nyvepria?” and the Product Monograph for the list of ingredients in Nyvepria.
- You are allergic to other medicine made using the bacteria *Escherichia coli*. Talk to your doctor if you have any questions about this information.

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

- Nyvepria can reduce the risk of infection, but it may not prevent all infections. An infection can still happen during the short time when your white blood cell levels are low. You and your caregivers must be alert and look for some of the common signs of infection, such as fever, chills, rash, sore throat, diarrhea, or redness, swelling, or pain around a cut or sore. If you notice any of these symptoms during treatment with Nyvepria, tell your doctor or nurse immediately.
- If there is a lump, swelling, or bruising at the injection site that does not go away, talk to your doctor. Occasionally, a problem may develop at the injection site.
- If you have sickle cell trait or sickle cell disease, tell your doctor prior to treatment. If you develop left upper abdominal pain or pain at the tip of your shoulder, tell your doctor or nurse immediately.

Other warnings you should know about:

Your doctor will decide if you are able to give yourself a subcutaneous (i.e., under the skin) injection. Nyvepria should only be injected on the day the doctor has determined for you, and should not be injected until 24 hours after receiving your last dose of chemotherapy in each cycle.

If you are injecting someone else with Nyvepria, it is important that you inform yourself about Nyvepria to know how and when to give the Nyvepria injection.

Make sure your doctor knows about all medications you are taking before starting Nyvepria injections. Patients taking lithium may need more frequent blood tests.

More information about Nyvepria is available in the Product Monograph. Any questions should be discussed with your doctor.

Pregnancy or breast-feeding and Nyvepria

Nyvepria has not been studied in pregnant women, and its effects on developing babies are not known. It is possible that Nyvepria can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breast-feeding, you should consult your doctor before using Nyvepria.

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 Nyvepria:

Drug interactions between Nyvepria 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 Nyvepria.

How to take Nyvepria:

Usual dose:

The recommended dosage of Nyvepria is a single subcutaneous injection, just under the skin, of 6 mg / 0.6 mL (the contents of one prefilled syringe), administered once per cycle of chemotherapy. You must wait at least 24 hours after your course of cancer chemotherapy before injecting Nyvepria.

Overdose:

If you think you, or a person you are caring for, have taken too much Nyvepria, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

As there should be a two-week period between Nyvepria and your next course of cancer chemotherapy, if you miss a planned dose, consult your doctor before taking the missed dose.

How to Prepare and Give Nyvepria Injection

Nyvepria is available in a prefilled syringe. Nyvepria should be stored in its carton to protect it from light until use. If you are giving someone else Nyvepria injections, it is important that you know how to inject Nyvepria.

Before a Nyvepria injection is given, always check to see that:

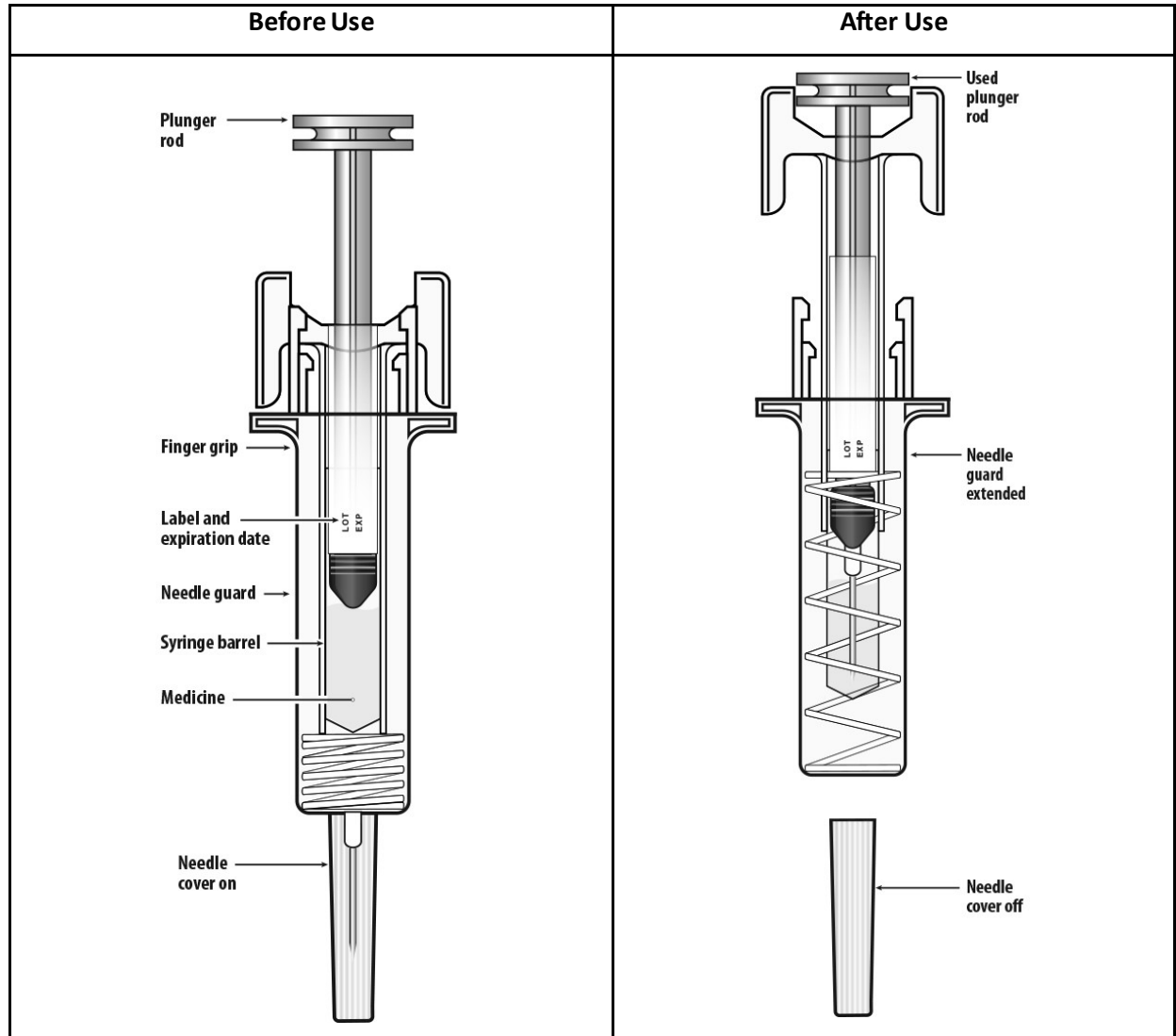
- The name Nyvepria appears on the carton and prefilled syringe label.
- The expiration date on the prefilled syringe has not passed. You should not use a prefilled syringe after the expiry date on the label.

- The Nyvepria liquid should always be clear and colourless. Do not use Nyvepria if the contents of the prefilled syringe appear discoloured or cloudy, or if the prefilled syringe appears to contain lumps, flakes, or particles.

IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

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

Guide to parts



Important: The needle is covered by the needle cover before use.

Read the Patient Medication Information for important information that you need to know about Nyvepria before using these Instructions for Use.

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

Using the Prefilled Syringe

- **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 Nyvepria appears on the carton and prefilled syringe label.
- Check the carton and prefilled syringe label to make sure the dose strength is 6 mg.
- **Do not** use a prefilled syringe after the expiration date on the label.
- **Do not** shake the prefilled syringe.
- **Do not** remove the needle cover from the prefilled syringe until you are ready to inject.
- **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.
- The prefilled syringe has a needle guard that automatically activates to cover the needle after the injection is given. **Do not** use a prefilled syringe if the needle guard has been activated. Use another prefilled syringe that has not been activated and is ready to use.

Call your healthcare provider if you have any questions.

Step 1: Prepare

A. Remove the prefilled syringe carton from the refrigerator.

Remove the inner syringe carton from the outer prefilled syringe carton by peeling away the cover. On a clean, well-lit surface, place the inner syringe carton at room temperature for **30** minutes before you give an injection.

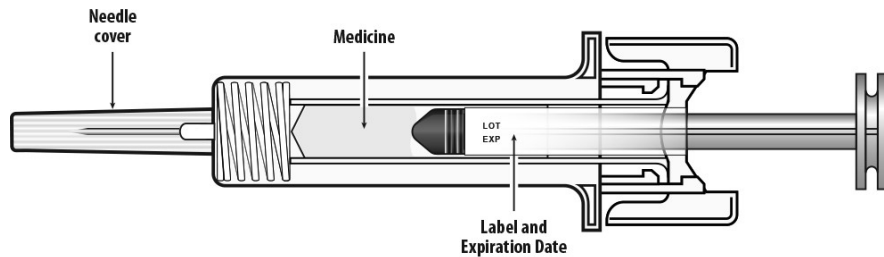
- **Do not** use the prefilled syringe if the inner syringe carton is damaged.
- **Do not** try to warm the prefilled syringe by using a heat source such as hot water or microwave.
- **Do not** leave the prefilled syringe in direct sunlight.
- **Do not** shake the prefilled syringe.

Open the inner syringe carton by peeling away the cover. Grab the needle guard to remove the prefilled syringe from the inner syringe carton.

For safety reasons:

- **Do not** grab the plunger rod.
- **Do not** grab the needle cover.

B. Inspect the medicine and prefilled syringe.



Make sure the medicine in the prefilled syringe is clear and colourless.

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

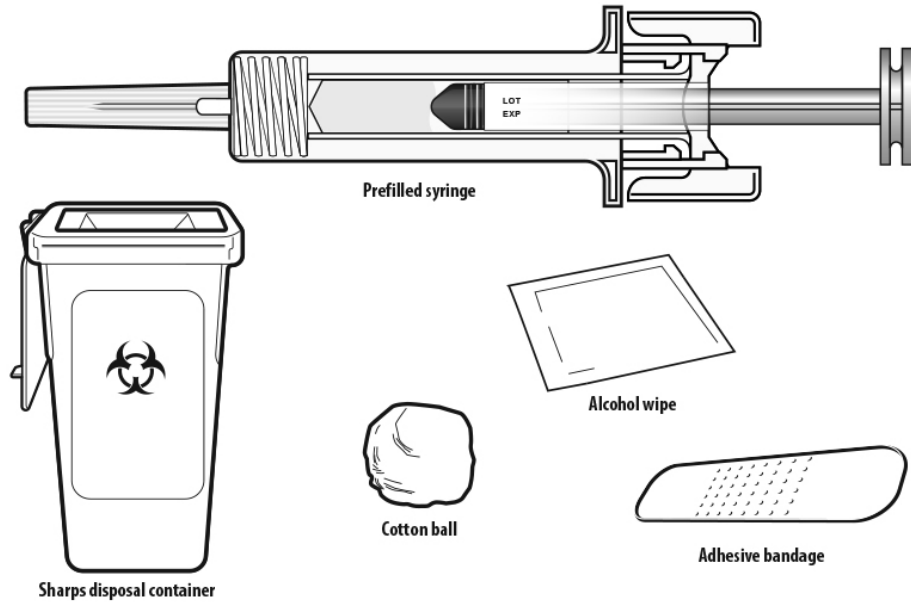
In all cases, use a new prefilled syringe and call your healthcare provider.

C. Gather all materials needed for the injection.

Wash your hands thoroughly with soap and water.

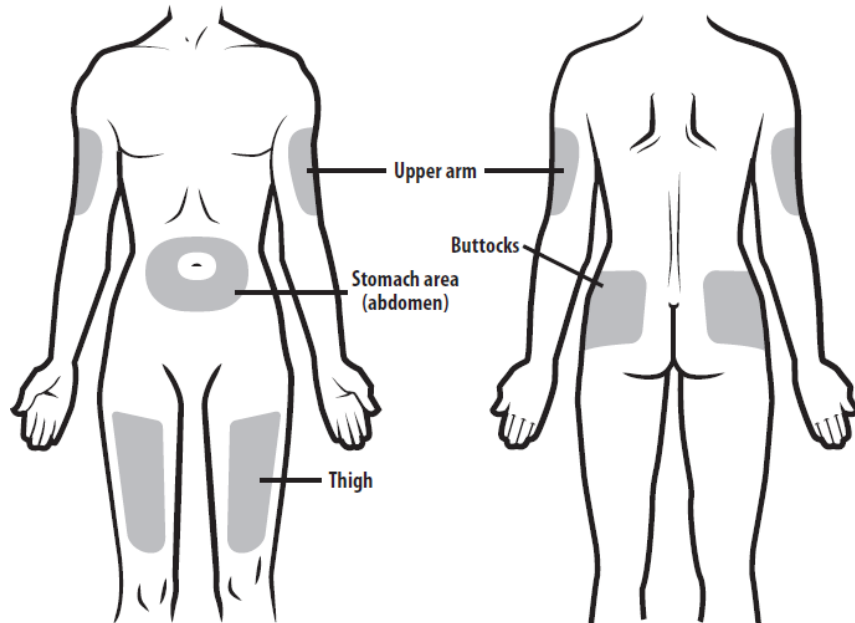
On a clean, well-lit work surface, place the:

- Prefilled syringe
- Alcohol wipe
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



Step 2: Get Ready

D. Prepare and clean the injection site(s).



You can use:

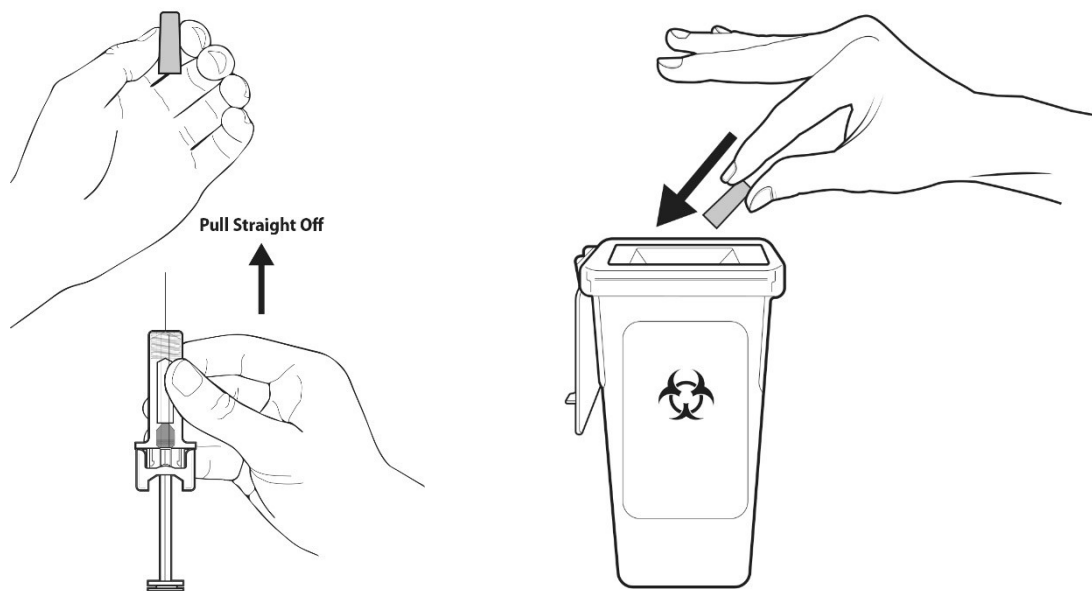
- Thigh
- Stomach area (abdomen), except for a 2-inch area right around the navel (belly button)
- Upper outer area of the buttocks (only if someone else is giving you the injection)
- Outer area of upper arm (only if someone else is giving you the injection)

Clean the injection site with an alcohol wipe. Let the 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 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.

E. Hold the prefilled syringe by the needle guard. Carefully pull the needle cover straight off and away from the body. Throw away the needle cover into the sharps disposal container. **Do not recap.**



- **Do not** remove the needle cover from the prefilled syringe until you are ready to inject.
- **Do not** twist or bend the needle cover.
- **Do not** hold the prefilled syringe by the plunger rod.
- **Do not** put the needle cover back onto the prefilled syringe.

Important: Throw the needle cover into the sharps disposal container.

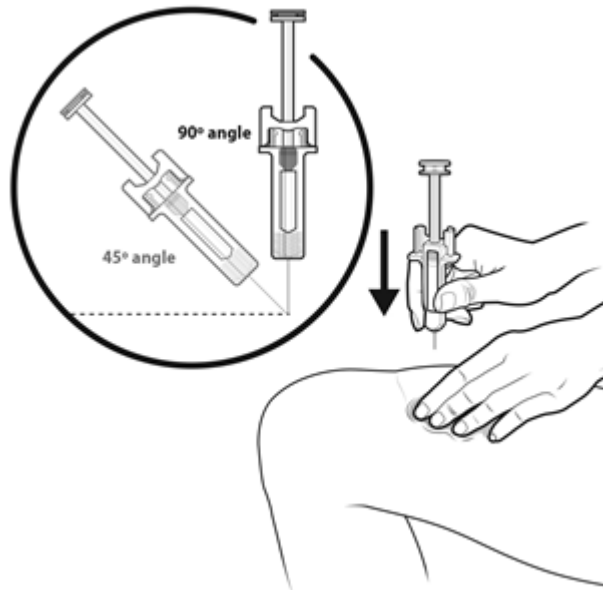
Step 3: Subcutaneous (under the skin) Injection

F. Pinch the injection site to create a firm surface.



Important: Keep skin pinched while injecting.

G. Hold the pinch. Insert the needle into the skin at 45 to 90 degrees.

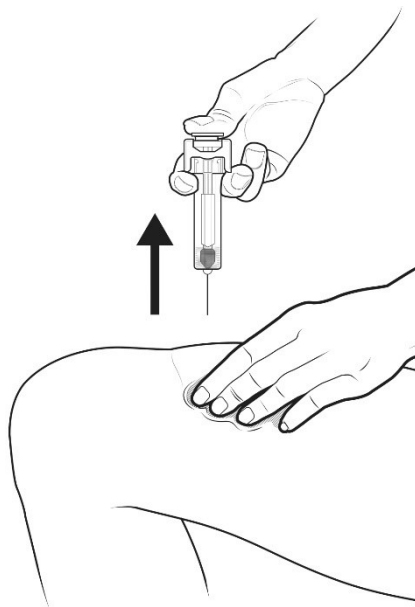


H. Using slow and constant pressure, push the plunger rod down until it reaches the bottom.

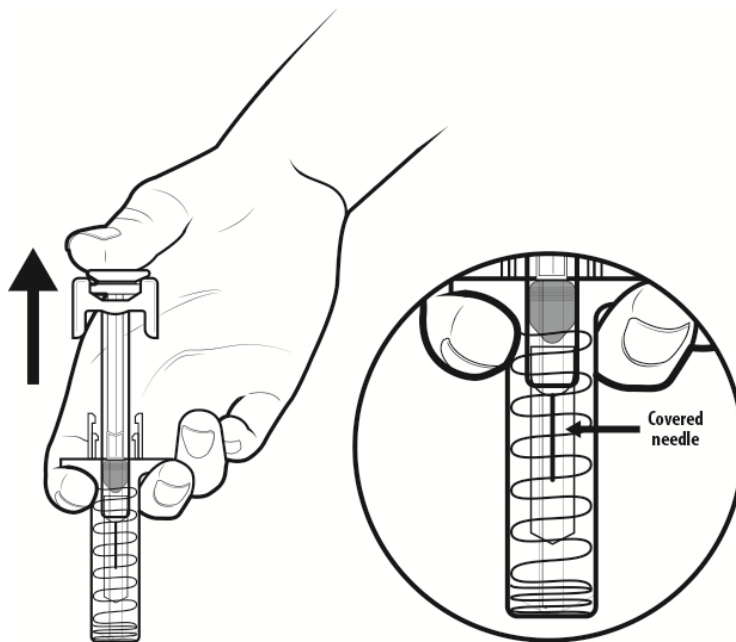


Step 4: Finish

I. When the syringe is empty, gently pull the syringe off the skin.

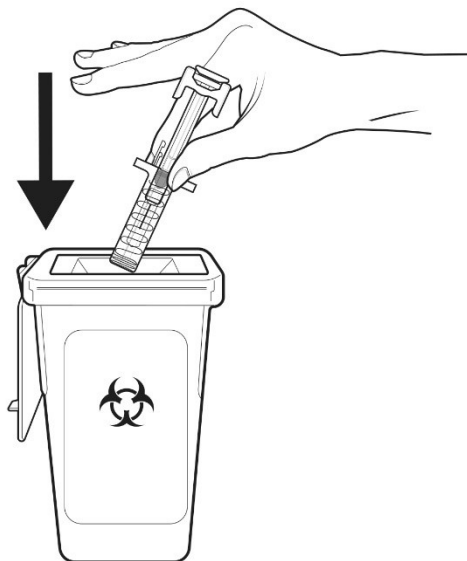


J. As you let go of the plunger rod, the needle guard will automatically slide over the needle until the needle is completely covered and the needle guard locks into place. **Do not recap the needle.**



Important: When you remove the syringe, if it looks like the medicine is still in the syringe barrel, this means you have not received a full dose. Call your healthcare provider right away.

K. 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 the disposal of used needles and 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.

L. Examine the injection site.

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

What are possible side effects from using Nyvepria?

These are not all the possible side effects you may feel when taking Nyvepria. If you experience any side effects not listed here, contact your healthcare professional. Please also see **Serious Warnings and Precautions**.

Spleen Rupture. Your spleen may become enlarged and can rupture while taking Nyvepria. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area. This pain could mean your spleen is enlarged or ruptured.

Serious Allergic Reactions. Serious allergic reactions can also happen. These reactions may cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, or sweating. If you experience an allergic reaction during the injection of Nyvepria, the injection should be stopped immediately. If at any time a serious allergic reaction occurs, immediately call a doctor or emergency services (for example, call 911).

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

Kidney injury (glomerulonephritis) has been seen in patients who received Nyvepria. Call your doctor immediately if you experience puffiness in your face or ankles, blood in your urine or brown coloured urine, or if you notice that you urinate less often than usual.

The most common side effect that you may experience is aching in the bones and muscles. If this occurs, it can usually be relieved with a non-acetylsalicylic acid over-the-counter pain reliever. Ask your doctor which is the most suitable one for you.

Some patients experience redness, swelling, or itching at the site of injection. This may be an allergy to the ingredients in Nyvepria, or it may be a local reaction. If you notice any of these signs or symptoms, call your doctor.

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			
Bone Pain		√	
UNCOMMON			
Low platelet counts (thrombocytopenia) (including the following symptoms: easy bruising and increased bleeding).		√	
Allergic Reactions (including the following symptoms): rash over the whole body, shortness of breath, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, weakness, sweating; severe redness or swelling or itching at injection site		√	√
Acute Respiratory Distress Syndrome (including the following symptoms: fever, shortness of breath, cough, or congestion in your lungs)		√	
VERY RARE			
Splenomegaly (including the following symptoms: pain in the left upper stomach area or left shoulder tip area)		√	
*FREQUENCY NOT KNOWN			
Splenic Rupture (including the following symptoms: left		√	

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	
upper abdominal pain or pain at the tip of your shoulder)			
Cutaneous Vasculitis (including the following symptoms: A rash in the skin surface that looks like purple or red spots or bumps, clusters of small dots, splotches or hives. Your skin may also be itchy.)		√	
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		√	
Kidney Injury (glomerulonephritis) (including the following symptoms): puffiness in your face or ankles, blood in your urine or brown coloured urine, or if you notice that you urinate less often than usual.		√	√
**Abnormal number of immature bone marrow cells (myelodysplastic syndrome) that could lead to a type of cancer (acute myeloid leukemia) (including the following symptoms: fever, bone pain, bruising, difficulty breathing, bleeding and a general feeling of tiredness).		√	√

*Reported in the post-marketing setting where the incidence is not known.

**Adverse events in breast and lung cancer patients receiving chemotherapy and/or radiotherapy

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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.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 Nyvepria after the expiry date which is stated on the outer carton and the label of the prefilled syringe.

- Nyvepria should be stored in the refrigerator between 2°C to 8°C but not in the freezer. Avoid shaking.
- If Nyvepria 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.
- Nyvepria can be left out at room temperature (not above 25°C) for a single period of up to 15 days that ends within the labeled expiry date. Once Nyvepria has been out at room temperature, it should not be placed back into the refrigerator. Any Nyvepria syringes that have been out of the refrigerator for longer than 15 days should not be used and should be disposed of in accordance with local requirements.
- Keep Nyvepria in the carton to protect from light or physical damage. Do not leave Nyvepria 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 Nyvepria 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 Nyvepria:

- 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: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug->

[product-database.html](#)); the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC

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