

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrArmlupeg™

Pegfilgrastim Injection

Sterile Solution, 6 mg (10 mg/mL)

Subcutaneous Use Only

Professed Standard

Hematopoietic Agent
Granulocyte Colony-Stimulating Factor

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

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Pr **Armlupeg™** (pegfilgrastim injection) is a biosimilar biological drug (biosimilar) to Neulasta.®

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between Armlupeg and the reference biologic drug Neulasta.

Armlupeg (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.

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

Armlupeg (pegfilgrastim) is contraindicated in patients with known hypersensitivity to *E. coli*-derived products, pegfilgrastim, filgrastim, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, **see 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

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

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. (**see 1.1 Pediatrics**).

4.3 Reconstitution

Not applicable. Product does not need to be reconstituted.

4.4 Administration

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

Armlupeg should not be vigorously shaken.

Following administration of Armlupeg from the single-use prefilled syringe, the patient should activate the UltraSafe® Plus Passive Needle Guard by placing their hands behind the needle, grasping the guard with one hand, and sliding the guard forward until the needle is completely covered and the guard clicks into place. NOTE: If an audible click is not heard, the needle guard may not be completely activated.

4.5 Missed Dose

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

5 OVERDOSAGE

The maximum tolerated dose of Armlupeg (pegfilgrastim) has not been determined in humans. Pegfilgrastim administered at a dose of 300 mcg/kg (n = 12), approximately three 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 recognize 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)	sorbitol, glacial acetic acid, sodium acetate trihydrate, polysorbate 20, and water for injection

Armlupeg is a sterile, clear, colourless, preservative-free solution for subcutaneous administration, presented as single-dose prefilled syringe (PFS) which contains 6 mg of pegfilgrastim (based on protein mass only) in 0.6 mL solution for injection. The pH of the product is pH 4.00 ± 0.20.

Availability of Dosage Forms

Armlupeg is supplied as a preservative-free solution (0.6 mL) containing 6 mg of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 27 gauge, ½ inch needle, with an UltraSafe® Plus Passive Needle Guard.

The needle cover on the single-use prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions and should not be handled by individuals who are sensitive to latex.

To reduce the risk of accidental needle sticks to users, each single-use prefilled syringe is equipped with an UltraSafe® Plus Passive Needle Guard that is manually activated to cover the needle during disposal.

Armlupeg is provided in a dispensing pack containing one syringe.

Description

Armlupeg (pegfilgrastim) is a biosimilar biological drug that is a long-acting form of recombinant human granulocyte colony-stimulating factor (r-metHuG-CSF) or filgrastim. Armlupeg is composed of filgrastim with a 20,000 dalton polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons; Armlupeg has a total molecular weight of 39,000 daltons.

7 WARNINGS AND PRECAUTIONS

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

General

Armlupeg (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 Armlupeg 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 Armlupeg 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, Armlupeg 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 Armlupeg have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas), mitomycin C, or myelosuppressive doses of anti-metabolites such as 5-fluorouracil (5-FU). Concomitant use of Armlupeg with 5-FU or other anti-metabolites has not been evaluated in humans, although it has been studied and shown to potentiate myelosuppression in animal models (see **16 NON-CLINICAL TOXICOLOGY**).

The safety and efficacy of Armlupeg 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 Armlupeg.

Potential Effect on Malignant Cells

Armlupeg (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 Armlupeg can act as a growth factor for any tumour type cannot be excluded. The use of pegfilgrastim 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 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 Armlupeg 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 Armlupeg 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 rechallenge, 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 Armlupeg should be discontinued. Antibodies to filgrastim or pegfilgrastim have been reported, although no neutralizing antibodies have been reported (see **8 ADVERSE REACTIONS: 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. 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.

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 Armlupeg who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Armlupeg should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Sexual Function/Reproduction

No studies evaluating sexual function or reproduction in humans were conducted with Armlupeg.

7.1 Special Populations

7.1.1 Pregnant Women

There were no pregnant women exposed to pegfilgrastim in clinical trials. Armlupeg should be used during pregnancy only if the potential benefit outweighs the risk to the fetus (see **16 NON-CLINICAL 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, Armlupeg is not recommended for women who are breast feeding. Armlupeg should only be administered to a nursing woman if the potential benefit outweighs the risk.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and effectiveness of Armlupeg in pediatric patients have not been established.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Of the total number of subjects with cancer who received pegfilgrastim in clinical studies (n = 930), 139 subjects (15%) were 65 years or older and 18 subjects (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 Armlupeg 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 drug 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 1 and 2.

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%)

Body System and Preferred Term	Pegfilgrastim (n = 465)	Filgrastim (n = 331)
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%)

Body System and Preferred Term	Pegfilgrastim (n = 467)	Placebo (n = 461)
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.

8.3 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 has 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 Armlupeg, see **14.3 CLINICAL TRIALS: 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**)
- Aortitis (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**)
- Capillary Leak Syndrome (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular**)
- 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**)
- Allergic reactions (see **7 WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity/Allergic Reactions**)
- Cutaneous Vasculitis (see **7 WARNINGS AND PRECAUTIONS, Immune**)
- Glomerulonephritis (see **7 WARNINGS AND PRECAUTIONS, Renal**)
- Acute respiratory distress syndrome (ARDS) (see **7 WARNINGS AND PRECAUTIONS, Respiratory**)
- Injection site reactions (pain, induration, and local erythema)
- Generalized erythema and flushing
- Sweet's syndrome (acute febrile neutrophilic dermatosis)

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

No serious drug interactions have been identified.

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

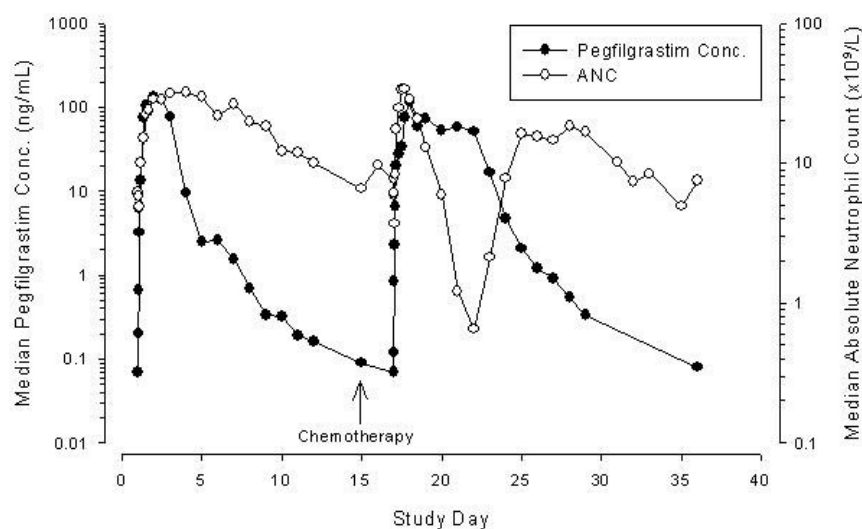
The pharmacokinetics and pharmacodynamics of pegfilgrastim were studied in patients with cancer. The pharmacokinetics of pegfilgrastim were nonlinear in cancer patients and clearance decreased with increases in dose. Neutrophil-mediated clearance is an important component of the clearance of pegfilgrastim, 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. 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_{1/2}	AUC_{0-∞}	Clearance
Single dose* Median	78.3-175 ng/mL	25-49 hr	5640-15000 ng·hr/mL	6.68-17.7 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. Health Canada has not authorized an indication for pediatric use.
- **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

Armlupeg (pegfilgrastim) should be stored refrigerated at 2° to 8°C (36° to 46°F). Keep the container in the outer carton to protect from light. Before injection, Armlupeg may be allowed to reach room temperature for a maximum of 48 hours. Armlupeg left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen Armlupeg should be allowed to thaw in the refrigerator before administration. If frozen a second time, Armlupeg should be discarded.

Armlupeg should be visually inspected for discolouration and particulate matter before administration. Armlupeg should not be administered if discolouration or particulates are observed.

12 SPECIAL HANDLING INSTRUCTIONS

Armlupeg (pegfilgrastim) should not be vigorously shaken.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	pegfilgrastim
Chemical name:	Recombinant N-(3-hydroxypropyl) methionylcolony-stimulating factor (human), 1-ether with alpha-methyl-omega-hydroxypoly (oxyethylene)
Molecular formula and molecular mass:	$(C_2H_4O)_n C_{845}H_{1339}N_{223}O_{243}S_9$ Pegfilgrastim has a total molecular weight of 39,000 daltons.
Structural formula:	Pegfilgrastim is composed of filgrastim (recombinant methionyl human G-CSF) with a 20,000 dalton polyethylene glycol (PEG) 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.

Product Characteristics

Armlupeg (pegfilgrastim) is a sterile, clear, colourless liquid.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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

- A randomized, double-blind, two-way cross over comparative pharmacokinetic (PK)/ pharmacodynamic (PD) study in healthy adult, volunteers (ALR/18/360/LBC-19-146)
- An open-label, randomized, comparative clinical study to assess immunogenicity in patients with breast cancer receiving myelosuppressive chemotherapy (LRP/PegGCSF/2016/004)

An overview of the study design and demographic characteristics of subjects enrolled in each clinical study is presented in Table 5.

Table 5 – Summary of Trial Design and Patient Demographics

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
ALR/18/360/LB C-19-146	Double-blind, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover PK, PD study in healthy, adult, human subjects	Single subcutaneous dose of Armlupeg and US-licensed Neulasta, 6 mg / 0.6 ml Duration: 14 days Washout period: at least 42 days	Randomized: 268 (264 dosed) Received both Armlupeg and Neulasta and completed study: 218	34.5 (18 – 44 years)	Male: 169 Female :95
LRP/PegGCSF /2016/004	Open-label, randomized, comparative, parallel group, two-arm, multicenter clinical study to assess the immunogenicity of Armlupeg versus Neulasta in breast cancer patients receiving myelosuppressive chemotherapy	Single subcutaneous dose of Armlupeg or US-licensed Neulasta, 6 mg / 0.6 ml	138 (70 Armlupeg, 68 Neulasta)	51.1 (29-75) years	Female

PK: Pharmacokinetics, PD: Pharmacodynamics, US = United States

Comparative Safety

In an open-label immunogenicity study (LRP/PegGCSF/2016/004), female patients with breast cancer receiving myelosuppressive chemotherapy were randomized 1:1 to receive either Armlupeg or US-Neulasta administered on Day 2/3 of each chemotherapy cycle of 21 days for up to 4 cycles. No differences in the safety between Armlupeg and US-Neulasta were observed in the breast cancer patients under the study conditions.

14.3 Comparative Bioavailability Studies

PK and PD comparability of Armlupeg and Neulasta was evaluated in a single-dose, two-way cross over comparative study (ALR/18/360/LBC-19-146) in healthy adult subjects with a single subcutaneous administration of Armlupeg and the reference biologic drug (US-licensed Neulasta).

Pharmacokinetics

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

Table 6 – Study ALR/18/360/LBC-19-146: Analysis of Primary PK Parameters

(Pegfilgrastim 6mg/0.6ml subcutaneous injection) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Armlupeg ¹ N = 218	US-Neulasta ² N = 218	% Ratio of Geometric Means	90% Confidence Interval
AUC _{0-t} (pg*h/ml)	8766542.8 11233917.9 (66.9%)	9175470.7 11529152.3 (64.43%)	94.8	89.9-100.0
AUC _{0-∞} (pg*h/ml)	8803955.8 11270017.4 (66.8%)	9213400.3 11559388.1 (64.3%)	94.9	90.0-100.0
C _{MAX} (pg / ml)	233006.5 281978.1 (57.7%)	245739.1 292009.3 (55.3%)	94.4	89.5-99.5
T _{MAX} (h)	20.8(40.4%)	20.5 (37.8%)	Not applicable	Not applicable
T _½ (h)	25.3 (56.2%)	28.8 (110.0%)	Not applicable	Not applicable

1. Armlupeg (Pegfilgrastim) by Lupin Pharma

2. US-Neulasta (Pegfilgrastim) by Amgen Inc

AUC_{0-t} = Area under the serum concentration-time curve measured from the time of dosing to the last measurable concentration

AUC_{0-∞} = Area under the serum concentration-time curve measured from the time of dosing and extrapolated to infinity

C_{max} = maximum concentration

T_{max} = time to C_{max}. T_{max} is expressed as the arithmetic mean (CV%).

T_{1/2} = half-life. T_{1/2} is expressed as the arithmetic mean (CV%).

Pharmacodynamics

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

Table 7 – Study ALR/18/360LBC-19-146: Analysis of Primary Pharmacodynamic Parameters [absolute neutrophil count (ANC)]

(Pegfilgrastim 6mg/0.6ml subcutaneous injection) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test¹	Reference²	% Ratio of Geometric Means	95% Confidence Interval³
ANC_AUEC _(0-tlast) (hr*10 ⁹ /L)	5836.0 6015.9 (23.8%)	5822.9 6013.3(22.54%)	100.2	98.7-101.8
ANC_C _{max} (10 ⁹ /L)	36.4 38.0 (27.8%)	36.3 38.0 (27.9%)	100.3	98.4-102.3

1. Armlupeg (Pegfilgrastim) by Lupin Pharma

2. US-Neulasta (Pegfilgrastim) by Amgen Inc

ANC_AUEC_{0-t} = area under the effect ANC-time curve from time zero to the last measurable time point

ANC_C_{max} = maximum effect in ANC

Comparative Safety

Similar safety profiles between Armlupeg and Neulasta were observed in the PK-PD study in healthy volunteers (ALR/18/360/LBC-19-146).

14.4 Immunogenicity

A tiered approach was used for anti-drug (pegfilgrastim) antibody (ADA) testing. Immunogenicity was assessed using a validated electrochemiluminescence (ECL) assay against ADA. A cell-based assay was used to detect neutralizing antibodies.

ALR/18/360/LBC-19-146 (single dose cross-over study in healthy subjects)

In study ALR/18/360/LBC-19-146, ADA were assessed from blood samples collected at pre-dose and 336 hours post dose in each period. In the sequence group receiving Armlupeg in the first period, 36 out of 114 (31.6%) subjects were positive for treatment-emergent ADA. In sequence group receiving Neulasta in the first period, 23 out of 111 (20.7%) subjects were positive for treatment-emergent ADA. Among them, 3 out of 36 (8.3%) subjects were positive for neutralizing antibody in subjects receiving Armlupeg in the first period, and 5 out of 23 (21.7%) positive for neutralizing antibody in subjects receiving Neulasta in the first period.

LRP/PegGCSF/2016/004 (immunogenicity study in breast cancer patients)

In the immunogenicity study (LRP/PegGCSF/2016/004) in breast cancer patients receiving myelosuppressive chemotherapy, one (1.7%) patient in the Armlupeg and 3 (5.4%) patients in the Neulasta group had treatment-emergent ADA (defined as a shift from negative at baseline to positive post-treatment) which developed 1 to 9 weeks after study drug administration. No patients had positive ADA detected at the end of the study (Day 84). None of the binding antibodies were neutralizing.

14.5 Clinical Trials- Reference biologic drug

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 female, 4 male
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 female, 1 male
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**).

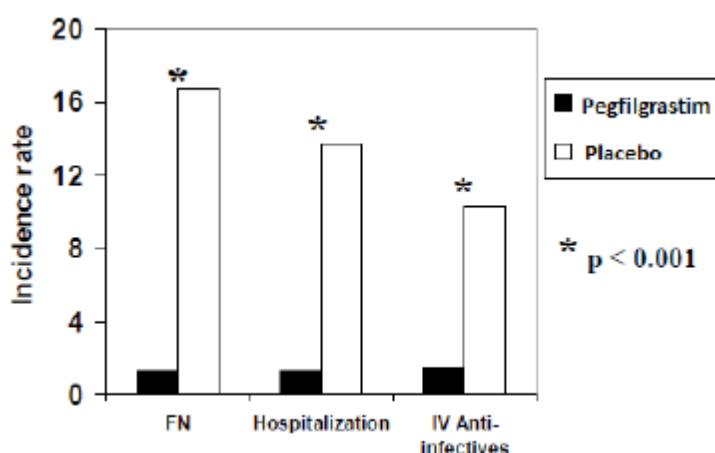
The third study employed a placebo control and evaluated the effect of pegfilgrastim on the

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%, $p \leq 0.001$). The incidence of hospitalizations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was 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 II 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

Preclinical Studies

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

The biological characteristic of Armluppeg and US-Neulasta was evaluated using a cell-based proliferation assay and a receptor binding assay, as outlined in Table 9.

Table 9 – Overview of Studies Comparing *In vitro* activity between Armluppeg and Neulasta.

	Test	Results for comparison
Receptor binding assays	G-CSFR binding assay (kinetics (k_a , k_d and K_D , Kinetics) and affinity (K_D , Equilibrium) of pegfilgrastim binding the G-CSF receptor)	Highly similar binding kinetics between Armluppeg and US-Neulasta was shown
<i>In vitro</i> bioactivity assay	<i>In vitro</i> proliferation assay (relative biological potency measured by stimulation of proliferation of M-NFS-60 cells)	Armluppeg and US-Neulasta displayed similar biological activity.

17 SUPPORTING PRODUCT MONOGRAPHS

NEULASTA (Pegfilgrastim Injection, Sterile Solution, 6 mg (10 mg/mL)), Submission Control No.: 242732, Product Monograph, Amgen Canada Inc. (JAN 08, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrARMLUPEG™ (pronounced *arm-loo-peg*)

pegfilgrastim injection

Read this carefully before you start taking **Armlupeg** 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 **Armlupeg**.

Armlupeg 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 Armlupeg. 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 Armlupeg 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 Armlupeg. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim.

What is Armlupeg used for?

Armlupeg 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 Armlupeg for you to increase the number of neutrophils (**nu**-tro-fils), which will fight infections.

Armlupeg is a long-acting form of granulocyte colony-stimulating factor (G-CSF), a substance naturally produced by the body.

How does Armlupeg work?

Armlupeg works by stimulating the bone marrow to make white blood cells. To make sure Armlupeg 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 Armlupeg?

Medicinal ingredients: pegfilgrastim

Non-medicinal ingredients: sorbitol, glacial acetic acid, sodium acetate trihydrate, polysorbate 20, and water for injection

The needle cover on the prefilled syringe contains a derivative of latex (dry natural rubber). If you

know you are allergic to latex, talk to your healthcare provider before using Armlupeg.

Armlupeg comes in the following dosage forms:

Armlupeg comes in a single-use pre-filled syringe with BD UltraSafe® Plus Passive Needle Guard, as a clear, colourless liquid solution. Each single-use syringe (0.6 mL) of Armlupeg (10 mg/mL) contains 6 mg of pegfilgrastim, the active substance.

Do not use Armlupeg if:

- You are allergic to pegfilgrastim, filgrastim, or any of the ingredients of Armlupeg. Check the section above **What are the ingredients in Armlupeg** and the Product Monograph for a list of ingredients in Armlupeg.
- You are allergic to other products 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 Armlupeg. Talk about any health conditions or problems you may have, including:

- If you have 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 Armlupeg, tell your doctor or nurse immediately. Armlupeg 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.
- 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 (ie, under the skin) injection. Armlupeg 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 Armlupeg, it is important that you inform yourself about Armlupeg to know how and when to give the Armlupeg injection.

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

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

Pregnancy or breast feeding and Armlupeg

Armlupeg has not been studied in pregnant women, and its effects on developing babies are not known. It is possible that Armlupeg 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 Armlupeg.

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 Armlupeg:

Drug interactions between Armlupeg 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 Armlupeg.

How to take Armlupeg:

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

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

- The name Armlupeg appears on the dispensing pack 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 Armlupeg liquid should always be clear and colourless. Do not use Armlupeg 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.

Guide to parts

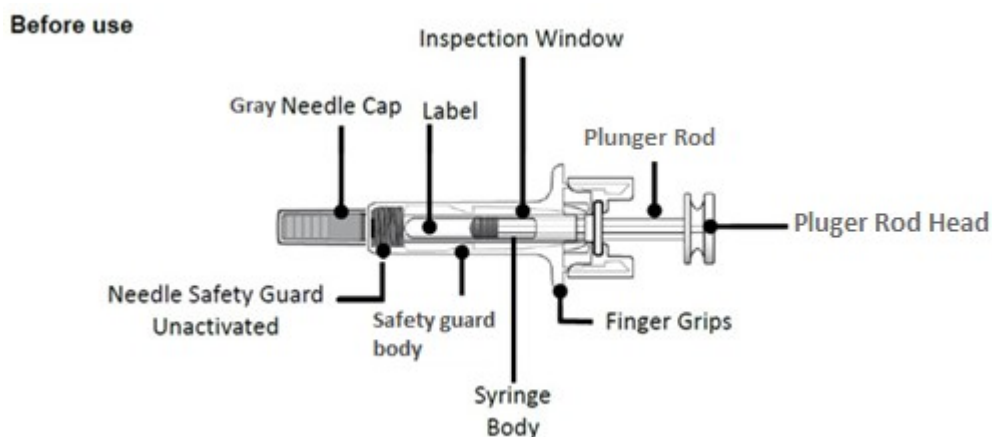


Figure 1

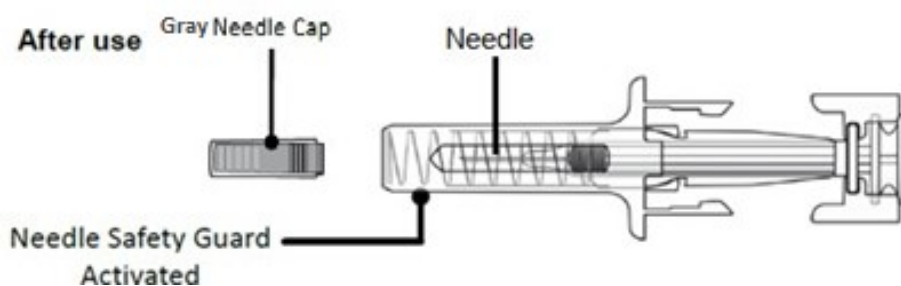


Figure 2

Important: The needle is covered by the gray needle cap before use.

Important

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

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

Storing the prefilled syringe

- Store Armlupeg in the refrigerator between 36°F to 46° F (2°C to 8°C).
- **Do not** freeze.
- Keep the prefilled syringe in the original carton to protect from light or physical damage.
- Take the prefilled syringe out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- Throw away (dispose of) any Armlupeg that has been left at room temperature, 68°F to 77°F (20°C to 25°C), for more than 48 hours.
- Keep the Armlupeg prefilled syringe out of the reach of children.

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 that the name Armlupeg appears on the carton and prefilled syringe label.
- Check the carton and prefilled syringe label to make sure the dose strength is 6 mg.
- You should not inject a dose of Armlupeg to children weighing less than 45 kg from a Armlupeg prefilled syringe. A dose less than 0.6 mL (6 mg) cannot be accurately measured using the Armlupeg prefilled syringe.
- **Do not** use a prefilled syringe after the expiration date on the label.
- **Do not** shake the prefilled syringe.
- **Do not** remove the gray needle cap 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.
- **Do not** attempt to activate the needle safety guard prior to injection.
- The gray needle cap on the prefilled syringe contains dry natural rubber (made from latex). **Tell your healthcare provider if you are allergic to latex. You should not give Armlupeg using the prefilled syringe if you have latex allergies**

Call your healthcare provider if you have any questions.

STEP 1: Prepare

A. Remove the prefilled syringe carton from refrigerator.
Put the original carton with any unused prefilled syringes back in the refrigerator.
Check the expiration date printed on the carton.

Important: **Do not** use if the expiration date has passed.

Remove the syringe tray from the carton. On a clean, well-lit surface, place the syringe tray at room temperature for **30** minutes before you give an injection.

- **Do not** remove the prefilled syringe from the original carton until you are ready to inject
- **Do not** use the prefilled syringe if the 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.

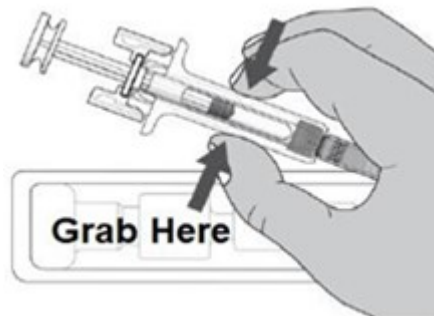


Figure 3

Open the tray by peeling away the cover. Grab the safety guard to remove the prefilled syringe from the tray. (See Figure 3)

For Safety reasons:

- **Do not** grab the plunger rod.
- **Do not** grab the gray needle cap.

B. Inspect the medicine and prefilled syringe.

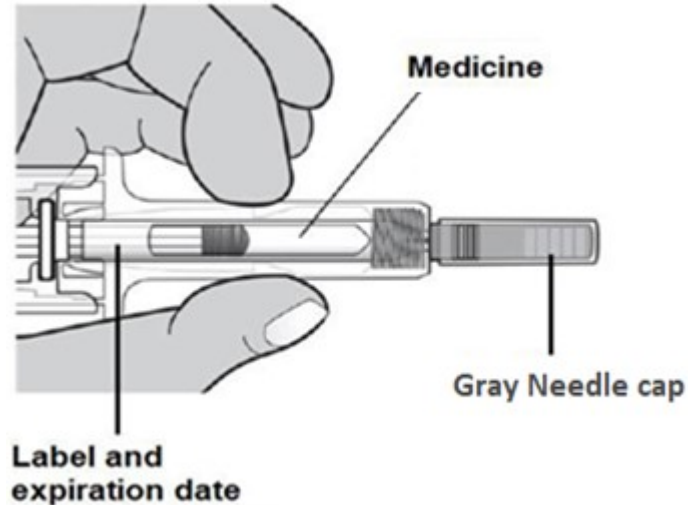


Figure 4

Make sure the medicine in prefilled syringe is clear and colorless (See Figure 4). It is normal to see one or more air bubbles in the syringe.

Do not use the prefilled syringe if:

- The medicine is cloudy or discolored or contains flakes or particles.
- Any part appears cracked or broken.
- The prefilled syringe has been dropped.
- The gray needle cap 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 injection (See Figure 5)

Wash your hands thoroughly with soap and water

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

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

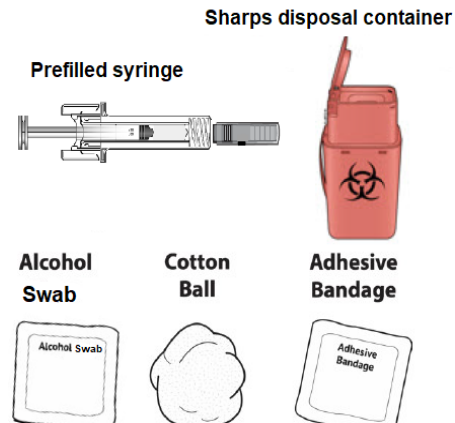


Figure 5

STEP 2: Get ready

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

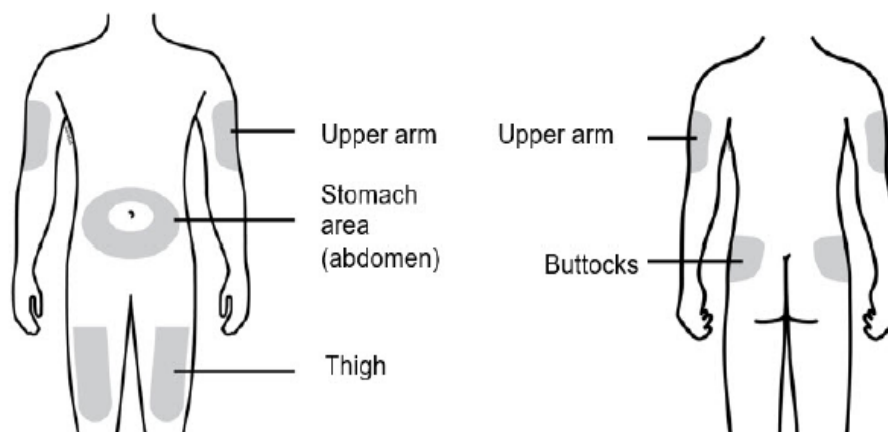


Figure 6

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 swab. Let the skin dry.

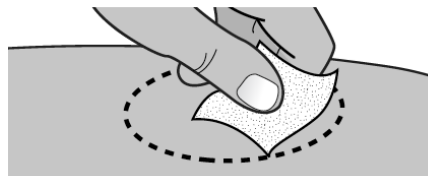


Figure 7

- **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 syringe barrel. Carefully pull the gray needle cap straight off and away from the body.

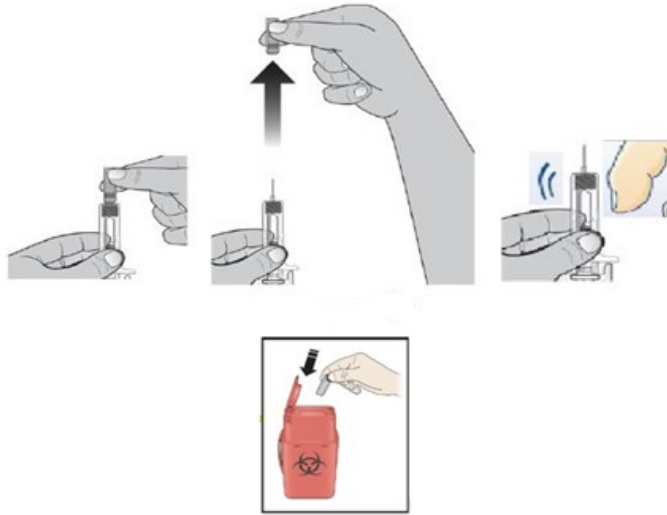


Figure 8

Remove the air bubble by tapping the syringe, if any. (See Figure 8)

- **Do not** remove the gray needle cap from the prefilled syringe until you are ready to inject.
- **Do not** twist or bend the needle cap.
- **Do not** hold the prefilled syringe by the plunger rod
- **Do not** put the gray needle cap back onto the syringe or never recap. In case, if the needle cap is removed accidentally and you are not ready for the injection, discard the opened syringe and use a new syringe when ready.
- **Do not** use the prefilled syringe if it has been dropped with the needle cap removed

Important: Throw the gray needle cap into the sharps disposal container.

STEP 3: Subcutaneous (under the skin) injection

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

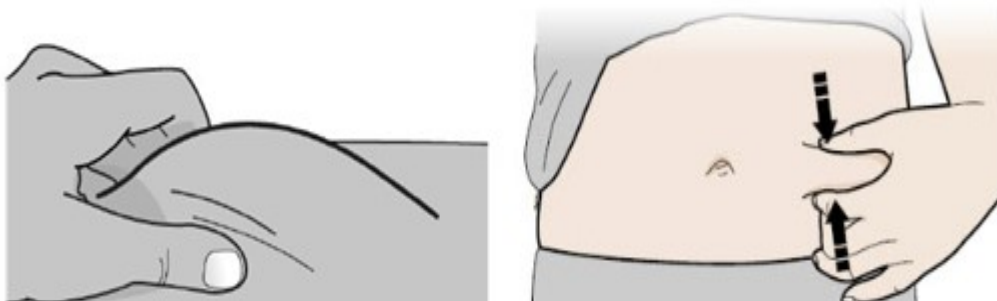


Figure 9

Important: Keep skin pinched while injecting

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

- **Do not** touch the plunger rod or grasp the syringe above the finger grips.

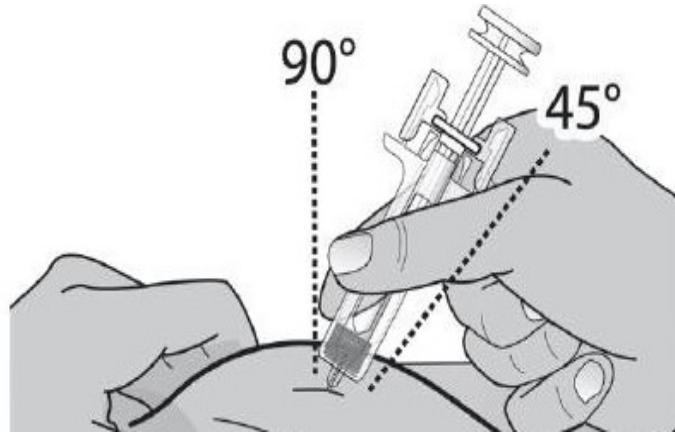


Figure 10

H. Using slow and constant pressure, push the plunger head until it reaches the bottom. This will ensure that you receive the full dose (injection is completed). (See Figure 11)

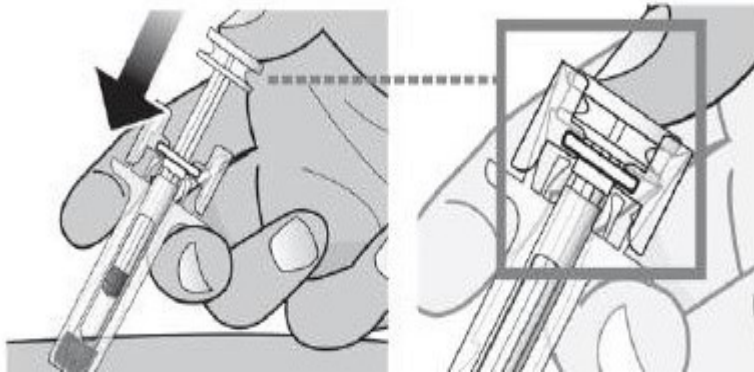


Figure 11

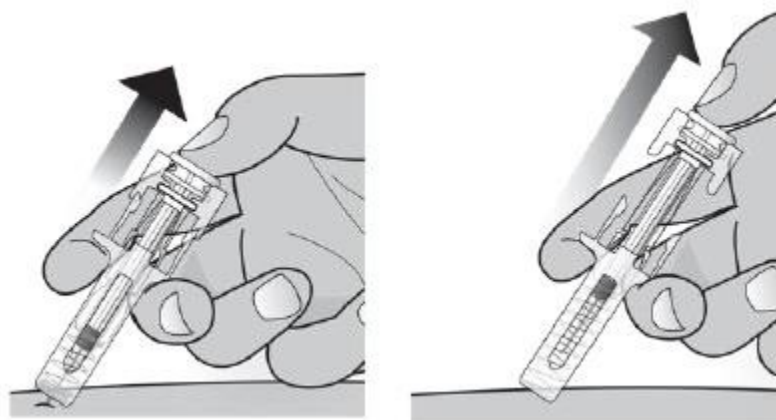


Figure 12

While the needle is still inserted, slowly move your thumb back, allowing the plunger rod to rise. This will release the needle safety guard to safely cover the needle. Then remove the syringe from the injection site. (See Figure 12)

Important: After the removal of the syringe if needle safety guard is not activated and/or if it appears that some medicine is still left in the syringe, this means you have not received a full dose. Call your healthcare provider right away.

STEP 4: Finish



Before you finish!

I. For your safety, ensure that the needle safety guard is activated i.e. needle is fully covered by needle safety guard.

Once the needle safety guard is extended, it will lock into position and will not slide back over the needle.

Important: Keep your hands away from the needle at all times.

J. Discard (throw away) the used prefilled syringe.



Figure 13

- Put the used prefilled syringe into a sharps disposal container right away after use (See Figure 13). **Do not** throw away (dispose of) the syringe in the household trash.
- If you do not have a cleared 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
 - 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.
- **Do not** reuse the prefilled syringe.
- **Do not** recycle prefilled syringes or sharps disposal container or throw them into household trash.

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

K. 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.

Usual dose:

The recommended dosage of Armlupeg is a single subcutaneous injection, just under the skin, of 6 mg (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 Armlupeg.

Overdose:

If you think you, or a person you are caring for, have taken too much Armlupeg, 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 Armlupeg and your next course of cancer chemotherapy, if you miss a planned dose, consult your doctor before taking the missed dose.

What are possible serious side effects of Armlupeg?

These are not all the possible side effects you may experience when taking Armlupeg. If you experience any side effects not listed here, tell your healthcare professional.

- **Spleen Rupture.** Your spleen may become enlarged and can rupture while taking Armlupeg. 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 Armlupeg, 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 Armlupeg. 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.

What are the most common side effects of Armlupeg?

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 Armlupeg, 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	
UNCOMMON $\geq 0.1\%$ and $< 1\%$			
Bone Pain		√	
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 $< 0.01\%$			
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 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.)		√	

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	
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 the face or ankles, blood in urine or brown coloured urine, or urinating 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:

Armlupeg should be stored in the refrigerator at 2° to 8°C (36° to 46°F), but not in the freezer. Keep the container in the outer carton to protect from light. Avoid shaking Armlupeg. If Armlupeg is accidentally frozen, allow it to thaw in the refrigerator before giving the next dose. However, if it is frozen a second time, do not use it and contact your doctor or nurse for further instructions. Armlupeg can be left out at room temperature for up to 48 hours. Keep out of reach of children. For any questions about storage, contact your doctor or nurse.

Keep out of reach and sight of children.

If you want more information about Armlupeg:

- 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 web site www.lupinpharma.ca, or by calling 514.866.3863.

This leaflet was prepared by Lupin Pharma Canada Ltd.

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