Drug Monograph

A - Drug Name

pegfilgrastim

COMMON TRADE NAME(S): Neulasta®; Lapelga™; Fulphila™; Ziextenzo®; Nyvepria™

- Different pegfilgrastim products are **not interchangeable**.
- For additional information on biosimilars, refer to:
  - Position Statements for the Clinical Operational Implementation of Oncology Biosimilars from the pan-Canadian Clinical Operations Working Group
  - Clinician Fact Sheet

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B - Mechanism of Action and Pharmacokinetics

Pegfilgrastim is a long-acting form of filgrastim, composed of filgrastim (recombinant human granulocyte colony-stimulating factor or G-CSF) covalently bonded to polyethylene glycol (PEG). Like filgrastim, pegfilgrastim regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions. Conjugation with PEG results in reduced renal clearance and prolonged duration of effect compared to filgrastim.

Absorption	The absorption of pegfilgrastim is largely dependent on the lymphatic system due to the attached PEG group contributing to the large size of the drug. It is slowly absorbed following subcutaneous administration.	
	Bioavailability	60-70% (subcut)
	T max	~ 1-2 days (subcut)
Distribution	Cross blood brain barrier?	unknown
	PPB	unlikely

Metabolism	It is not known if pegfilgrastim is metabolized. Once it binds to the therapeutic target, pegfilgrastim is internalized by the neutrophil and undergoes nonspecific degradation.	
Elimination	Pegfilgrastim has a self-regulating clearance and is mainly eliminated via a saturable neutrophil-mediated route. The clearance is dependent on the number of neutrophils and body weight of the patient: The clearance increases with increasing number of neutrophils and lower body weights.	
	Urine	minimal
	Half-life	25-49 hours (after subcut use)

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C - Indications and Status

Health Canada Approvals:

- Decrease the incidence of infection (i.e. febrile neutropenia) in patients with non-myeloid malignancies receiving myelosuppressive antineoplastic drugs.

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D - Adverse Effects

The following table contains adverse effects reported in patients with lymphoma and solid tumours (breast and thoracic) treated with pegfilgrastim following non-myeloablative chemotherapy, where the incidence was higher than placebo. It also includes severe, life-threatening and post-marketing adverse effects.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Other - aortitis (rare)	E
Dermatological	Cutaneous vasculitis (rare)	E
	Other (Sweet's syndrome; rare)	E

Hematological	Leukocytosis (> 100 x 10^9/L: <1%)	E
	Sickle cell crisis (in patients with sickle cell trait or disease; rare)	E
	Splenic rupture (+/- splenomegaly; rare)	E
	Thrombocytopenia (rare, may be severe)	E
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Injection site reaction (<1%)	I
Musculoskeletal	Musculoskeletal pain (13%)	E
Neoplastic	Leukemia (secondary) (rare)	D
Nervous System	Headache (1%)	E
	Other - hypertonia (<1%)	E
Ophthalmic	Other - periorbital edema (<1%)	E
Renal	Nephritis (glomerulonephritis) (rare)	E
Respiratory	Acute respiratory distress syndrome (ARDS) (rare)	E
Vascular	Capillary leak syndrome (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Across all studies, no life-threatening or fatal adverse events were attributed to pegfilgrastim and most adverse experiences were attributed as the sequelae of the underlying malignancy or cytotoxic chemotherapy. The most common adverse effects are **bone pain** and **muscle pain**. Bone pain was generally reported as mild-to-moderate, and could be controlled with non-narcotic analgesics in most patients.

Marked **leukocytosis** (>100 x 10^9 /L) has occurred occasionally. However, there were no reports of adverse clinical effects associated with this degree of leukocytosis.

Aortitis has been reported in patients receiving pegfilgrastim. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell).

Hypersensitivity reactions, including anaphylaxis, skin rash, urticaria have been described; these may occur on initial, subsequent, or re-challenge treatments. In rare cases, allergic reactions (including anaphylactic reactions) can recur within days after the discontinuation of initial anti-allergic treatment.

Cases of **glomerulonephritis** have been reported in patients receiving pegfilgrastim, usually resolving after dose reductions or withdrawal.

Rare **splenic rupture**, including fatal cases, have been reported following pegfilgrastim administration. Patients who report left upper abdominal or shoulder tip pain following pegfilgrastim use should be investigated for an enlarged spleen or splenic rupture.

Acute respiratory distress syndrome (ARDS) have occurred with pegfilgrastim use, possibly due to the influx of neutrophils to the inflammation sites on the lungs.

Capillary leak syndrome (CLS), characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration, has been reported and may be life-threatening. Prompt treatment is required.

An increased risk of **myelodysplastic syndrome** (MDS) and **acute myeloid leukemia** (AML) has been associated with pegfilgrastim when used in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer.

There have been reports of patients developing binding, but not neutralizing, antibodies to pegfilgrastim.

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E - Dosing

Refer to protocol by which patient is being treated.

Different pegfilgrastim products are **not interchangeable.**

Adults:

- 6 mg Subcut as a single dose given 24 to 72 hours post systemic treatment (once per cycle).
- Pegfilgrastim can be given with regimens that are administered every 14 days or more. There must be an interval of at least 12 days from the time of pegfilgrastim to the next dose of myelosuppressive systemic treatment; however, there may be exceptions depending on the treatment regimen and clinical trial protocol.

Also refer to the Clinical Practice Guideline - Prevention and Outpatient Management of Febrile Neutropenia in Adult Cancer Patients.

Dosage with Toxicity:

Toxicity	Pegfilgrastim Dose
Severe hypersensitivity or anaphylactic reaction	Discontinue
Capillary leak syndrome	
ARDS	
Aortitis	
Sickle cell crisis	
Alveolar hemorrhage	Hold until resolution or discontinue
Glomerulonephritis	Consider dose reduction or discontinue

May consider filgrastim for patients who experience severe musculoskeletal pain.

Dosage with Hepatic Impairment:

No information found. Changes in pegfilgrastim pharmacokinetics are not expected as the drug is mainly eliminated via neutrophil-mediated clearance.

Dosage with Renal Impairment:

No dose adjustment required in end-stage renal disease or renal impairment.

Dosage in the elderly:

No dose adjustment required. There were no overall differences in safety or effectiveness observed in pegfilgrastim treated patients ≥ 65 years of age compared to younger patients.

Children:

The safety and effectiveness of pegfilgrastim in pediatric patients have not been established.

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F - Administration Guidelines

Different pegfilgrastim products are **not interchangeable.**

- Available as a prefilled syringe for subcutaneous use only. Do not shake drug.
- Do not mix with any diluents.
- The pre-filled syringes for some pegfilgrastim products contain a derivative of latex which may cause allergic reactions in some people. Refer to the product monograph. These products should not be handled by individuals sensitive to latex.
- If a scheduled dose is missed and there is less than 12 days before the next dose of systemic treatment, the pegfilgrastim dose should not be given.
- Keep refrigerated; do not freeze. Protect from light.
- Refer to the respective product monograph(s) for stability information at room temperature before injection.

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to E. coli derived proteins, pegfilgrastim, filgrastim or any other components of the product

Other Warnings/Precautions:

- Pegfilgrastim has not been evaluated in use for peripheral blood progenitor cell mobilization and should not be used in that setting. The use of pegfilgrastim in chronic myeloid leukemia (CML) and MDS has not been studied.
- Since some cell lines (i.e. head and neck, lung, myeloid, T-lymphoid, bladder) express the G-

CSF receptor, the possibility of pegfilgrastim acting as a tumour growth factor cannot be excluded.

- Since patients are more likely to receive full dose chemotherapy with pegfilgrastim support, they may be at greater risk of thrombocytopenia, anemia and non-hematologic adverse effects of chemotherapy. Exercise caution when pegfilgrastim is administered with drugs that can lower platelet count.
- Patients with sickle cell disease (may precipitate sickle cell crisis).

Other Drug Properties:

- Carcinogenicity: Unlikely

Pregnancy and Lactation:

- Mutagenicity: No
- Embryotoxicity: Probable
  Pegfilgrastim should only be used during pregnancy if the potential benefit outweighs the risk to the fetus.
- Crosses placental barrier: Documented in animals
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Unlikely

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Lithium	Greater than expected increase in neutrophils	Potentiate release of neutrophils	Use with caution; more frequent monitoring of neutrophil counts
Bone imaging	Transient positive bone imaging changes	↑ hematopoietic activity in the bone marrow	Consider when interpreting bone imaging results
cytotoxics	↑ myelosuppression	↑ sensitivity of myeloid cells	Do not administer pegfilgrastim within 12 days before or within 24 hours after cytotoxics
antineoplastics with delayed myelosuppression	additive myeloproliferative effect	theoretically antagonist mechanism	Caution (unknown significance)

(e.g. nitrosourea derivatives) or mitomycin or myelosuppressive doses of antimetabolites

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, before chemotherapy, and as clinically indicated
Urinalysis	Baseline and as clinically indicated
Clinical assessment for bone pain, upper abdominal pain, hypersensitivity, pulmonary and dermatological effects, aortitis	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- pegfilgrastim - Lapelga brand
- pegfilgrastim - Fulphila brand
- pegfilgrastim - Ziextenzo brand
- pegfilgrastim - Nyvepria brand

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K - References

Clinical Practice Guideline - Prevention and Outpatient Management of Febrile Neutropenia in Adult Cancer Patients. Ontario Health (Cancer Care Ontario), 2021.

Filgrastim drug monograph, Ontario Health (Cancer Care Ontario) 2021.

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Prescribing Information: Neulasta® (pegfilgrastim). Amgen Inc. U.S. January 2021.

Product Monograph: Neulasta® (pegfilgrastim). Amgen Canada, January 8, 2021.

Yang BB, Kido A. Pharmacokinetics and pharmacodynamics of pegfilgrastim. Clin Pharmacokinet. 2011;50(5):295-306. doi:10.2165/11586040-000000000-00000.

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August 2022 Updated Mechanism of Action and Pharmacokinetics, Adverse Effects, and Dosage with Toxicity sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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