Drug Monograph

A - Drug Name

filgrastim

SYNONYM(S): G-CSF; Granulocyte-Colony Stimulating Factor

COMMON TRADE NAME(S): Neupogen®, Grastofil®, Nivestym®, Nypozi®

- Different filgrastim 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

G-CSF regulates the production of neutrophils within the bone marrow. It affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of cellular metabolism associated with respiratory burst, antibody-dependent killing, and increased expression of some cell surface antigens). Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology – but unlike the endogenous form, filgrastim is unglycosylated.G-CSF has been shown to have minimal direct in vivo or in vitro effects on the production of other hematopoietic cell types.

Absorption	Absorption showed a linear correlation between the parenteral dose and both the serum concentration and exposure.	
	Peak plasma levels	Within 2-8 hours (subcut administration)
	Onset	1-2 days
Distribution	Cross blood brain barrier?	Unknown

	PPB	Unlikely
Metabolism	It is suggested that the drug-GCSF receptor complex is internalized to the endosomal compartments, and is either recycled or degraded.	
Elimination	Clearance is dependent on filgrastim concentration and neutrophil count. Receptor-mediated processes appear to be an important route of elimination. G-CSF receptor-mediated clearance is saturated by high concentration of filgrastim and is diminished by neutropenia. In addition, filgrastim is cleared by the kidney.	
	Half-life	3.5 hours (average)

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C - Indications and Status

Health Canada Approvals:

- Cancer patients receiving myelosuppressive chemotherapy
- Patients with acute myeloid leukemia
- Cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation
- Cancer patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy

Refer to the product monographs for a full list and details or approved indications.

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D - Adverse Effects

The following table contains adverse effects reported in patients treated with filgrastim following combination chemotherapy in small cell lung cancer patients, where the incidence was higher than placebo. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (3%) (including myocardial infarctions and arrhythmias)	E
	Hypotension (4%) (mild, transient)	I
	Other - Aortitis (rare)	E
Dermatological	Erythema nodosum (rare) (in BMT)	E
	Other - Sweet's syndrome (rare)	E
	Rash, pruritus (6%)	E
General	Fever (12%)	E
Hematological	Leukocytosis (2%)	E
	Other - splenomegaly (1 to <10%)	E
	Sickle cell crisis (in patients with sickle cell trait or disease) (rare)	L
	Splenic rupture (rare)	D
	Thrombocytopenia (rare) (may be severe)	E
Hypersensitivity	Hypersensitivity (rare) (may be severe)	I
Injection site	Injection site reaction (rare)	I
Metabolic / Endocrine	↑ ALP (27-58%) (transient)	E
	Hyperuricemia (27-58%) (transient)	L
	↑ LDH (27-58%) (transient)	L
Musculoskeletal	Bone pain (medullary) (24%)	E
	Other - Chondrocalcinosis (rare)	E
Neoplastic	Leukemia (secondary) (2% in congenital neutropenia) (rare with chemotherapy and/or radiotherapy in patients with breast and lung cancer)	D
Renal	Nephritis (glomerulonephritis) (rare)	E
Respiratory	Acute respiratory distress syndrome (ARDS) (rare)	E
	Other - Alveolar hemorrhage (rare) (in healthy donors undergoing PBPC mobilization)	E
Vascular	Capillary leak syndrome (rare)	E D

	Vasculitis (cutaneous) (rare – mostly in severe chronic neutropenia) (may be severe)	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)

The most common side effects for filgrastim are **bone pain** and **muscle pain**.

Filgrastim generally is well tolerated, and only rarely have adverse effects been severe enough to require discontinuation of the drug.

Dose-dependent mild to moderate (occasionally severe) **medullary bone pain** was the only consistently reported adverse event across all cancer patient populations. The bone pain appears to be dependent on the dose and/or route of administration. In most reported cases, bone pain appeared to occur at sites containing bone marrow in the 2 to 3 day period preceding the increase in peripheral neutrophil count and to be particularly severe in patients with marked leukocytosis. Filgrastim-induced bone pain usually can be effectively prevented or treated with non-opioid oral analgesics (e.g., acetaminophen). In severe cases, opioid analgesics may be used. Bone pain generally resolves spontaneously with continued filgrastim therapy.

Intensified doses of chemotherapy may result in increased rates of toxicity for those agents (including secondary leukemias with alkylating agents).

Aortitis has been reported in patients receiving filgrastim. 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).

Cutaneous vasculitis has been reported most frequently in patients with severe chronic neutropenia receiving long-term filgrastim therapy. Adverse cutaneous effects appeared to be related to high neutrophil counts and resultant infiltration at sites of vascular inflammation that occurred as a result of filgrastim therapy.

Capillary leak syndrome (CLS), characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration, can cause circulatory shock and may be fatal. Prompt treatment is required.

Acute Respiratory Distress Syndrome (ARDS) may develop in patients with sepsis due to migration of neutrophils to lung inflammation sites

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.

Myelodysplastic syndrome (MDS) and **acute myeloid leukemia** (AML) have been associated with filgrastim in patients with chronic neutropenia and when used in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Abnormal cytogenetics and MDS are

associated with the eventual development of AML. The effects of filgrastim on the development of abnormal cytogenetics and the effect of continued filgrastim therapy in patients with abnormal cytogenetics are unknown.

Serious allergic reactions (including anaphylaxis) have been reported rarely, usually occurring within 30 minutes of exposure. Some reactions occurred on initial exposure and appeared to occur more frequently in patients receiving filgrastim intravenously. These reactions generally responded rapidly to antihistamine and corticosteroid treatment, but recurred in more than 50% of patients who were rechallenged.

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

Splenomegaly has been reported in patients who had received long-term therapy of filgrastim. Increases in spleen size were not associated with clinical manifestation in most patients, and partially resolved in some patients during continued therapy with the drug. Rarely, rapid increase in spleen size occurs and may lead to rupture.

Data suggest the development of binding antibodies to filgrastim in a small portion patients (3%). However, there was no evidence of a neutralizing antibody response.

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E - Dosing

Refer to protocol by which patient is being treated.

Different filgrastim products are **not interchangeable**.

Filgrastim should not be administered in the period 24 hours before to 24 hours after cytotoxic chemotherapy and/or marrow/stem cell transfusion.

For cancer patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy, the first dose of filgrastim should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after PBPC infusion.

Adults:

Chemotherapy-induced neutropenia:

- 5 mcg/kg/day (Subcut)

  OR

- 300 mcg (if < 90 kg) or 480 mcg (if ≥ 90 kg or < 90 kg if poor response to 300 mcg) Subcut daily starting 24-72 hours post systemic treatment
- When used with systemic treatment regimens that are administered ≥ 14 days apart, filgrastim treatment should typically be given for least 7 days (may consider 5 days for early breast cancer).
- For systemic treatment regimens that repeat < every 14 days, continue filgrastim until ANC recovery (or anticipated ANC recovery).
- Refer to the Clinical Practice Guideline - Prevention and Outpatient Management of Febrile Neutropenia in Adult Cancer Patients for more information.

Patients receiving myeloablative chemotherapy followed by bone marrow transplantation:

- 10 mcg/kg/day IV infusion over 4-24 hours, or continuous Subcut infusion over 24 hours.
- Doses may be adjusted according to ANC response as shown in Table 1.

Table 1:

ANC (x 10^9/L)	Filgrastim Dose
If > 1 for 3 consecutive days	Reduce to 5 mcg/kg/day. If ANC falls to < 1, ↑ to 10 mcg/kg/day.
THEN,	
If > 1 for 3 more consecutive days	Discontinue filgrastim.
If return to < 1	Resume at 5 mcg/kg/day.

Peripheral blood progenitor cell (PBPC) mobilization (cancer patients only)::

- Mobilization: 10 mcg/kg/day Subcut or continuous Subcut 24-hour infusion, given for at least 4 days before the first leukapheresis and continued to the day of the last leukapheresis.
    - Administration of filgrastim for 7 days with leukaphereses on days 5, 6, and 7 has been found to be safe and effective.
- After PBPC transplant: 5 mcg/kg/day given either Subcut or as an IV infusion. Titrate daily dose according to table 1.

Dosage with Toxicity:

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

Dosage with Hepatic Impairment:

No dosage adjustment necessary.

Dosage with Renal Impairment:

No dosage adjustment necessary.

Dosage in the elderly:

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

Children:

- The recommended dose in pediatric oncology patients receiving myelosuppressive chemotherapy is 5 mcg/kg/day Subcut. The safety profile of filgrastim in pediatric patients appears similar to that reported in adults.
- Safety in neonates has not been established.

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F - Administration Guidelines

Different filgrastim products are **not interchangeable**.

- Filgrastim is intended for subcutaneous injection or intravenous use and should not be given by any other route of administration.
- Subcutaneous self-administration (or administered by home caregiver) is possible; drug available by outpatient prescription.
- Some filgrastim 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 required, filgrastim may be diluted in D5W. DO NOT dilute with saline as precipitation may occur.
- Filgrastim diluted to a final concentration of 5-15 mcg/mL should be protected from adsorption of the drug to infusion containers or equipment, by adding **human albumin** to the solution at a concentration of 2 mg/mL.
- **Do not** dilute filgrastim to < 5 mcg/mL, even if human albumin is present in the solution.
- Refer to the product monograph(s) for information on compatibility with IV infusion containers or equipment.
- For IV administration, infuse over 15-30 minutes or as CIV.
- Refrigerate (2 to 8^{o}C) but do not freeze. Protect from light and avoid vigorous shaking.
- Accidental exposure to room temperature or exposure to freezing temperatures does not adversely affect the stability of filgrastim. It should be discarded if frozen more than once.
- 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 filgrastim, pegfilgrastim, or E. coli derived products or to any constituent of the product

Other Warnings/Precautions:

- PBPC mobilization in healthy donors is not an indicated use.
- Severe sickle cell crises have been reported with filgrastim use in patients with sickle cell trait or sickle cell disease.
- Use with caution in patients with pre-existing cardiac conditions.
- The safety and efficacy of filgrastim have not been established with simultaneous administration of radiation or chemotherapy (within 24 hours).
- Filgrastim may act as a growth factor for certain tumour types and use has not been fully investigated in CML and MDS. Caution should be exercised in using this drug in patients with CML or MDS.
- Since patients are more likely to receive full dose chemotherapy with filgrastim support, they may be at greater risk of thrombocytopenia, anemia and non-hematologic adverse effects of chemotherapy.
- Response to filgrastim may be diminished in patients with decreased neutrophil precursors, such as those who have extensive pre-treatment with chemotherapy or radiotherapy.

Other Drug Properties:

- Carcinogenicity: Unknown
  The carcinogenic potential of filgrastim has not been studied; the possibility that filgrastim can stimulate growth of any tumour type cannot be excluded.

Pregnancy and Lactation:

- Mutagenicity: No
- Embryotoxicity: Probable
  Filgrastim should only be used during pregnancy if the potential benefit outweighs the risk to the fetus.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended.
- Fertility effects: Unlikely

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cytokines (hematopoietic growth factors)	Additive myeloproliferative effect	Synergistic stimulation	Caution (unknown)
Antineoplastics with delayed myelosuppression (e.g. nitrosourea derivatives) or mitomycin or myelosuppressive doses of antimetabolite	Reduced effect or additive myeloproliferative effect (unknown)	Theoretically antagonistic mechanism	Caution (unknown)
Lithium	Additive myeloproliferative effect	Potentially release neutrophils	Caution
cytotoxics	↑ neutropenia	↑ sensitivity of neutrophils	Do not start Filgrastim treatment within 24 hours before or after chemotherapy
Bone imaging	transient positive bone imaging changes	↑ hematopoietic activity in bone marrow	Consider when interpreting bone imaging results.

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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 and 2-3 times a week during filgrastim therapy
Urinalysis	Baseline and as clinically indicated
Clinical assessment of bone pain, upper abdominal pain, hypersensitivity, aortitis, pulmonary, dermatological and cardiac effects	At each visit

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

Refer to the product monographs for monitoring in other non-oncologic indications.

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- filgrastim (biosimilars) - refer to ODB Formulary for details

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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.

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Prescribing Information: Neupogen® (Filgrastim). Amgen Inc. (US) 2021.

Product Monograph: Grastofil® (Filgrastim). Apotex Inc. September 29, 2021.

Product Monograph: Neupogen® (Filgrastim). Amgen Canada Inc., January 8, 2021.

Product Monograph: Nivestym™ (Filgrastim). Pfizer Canada ULC., April 16, 2020.

April 2025 Modified Administration Guidelines section

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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