DRUG NAME: Filgrastim

SYNONYM(S): Granulocyte colony stimulating factor (G-CSF)

COMMON TRADE NAME(S): NEUPOGEN®, GRASTOFIL® (biosimilar), NIVESTYM® (biosimilar), NYPOZI® (biosimilar)

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Filgrastim (recombinant human granulocyte colony stimulating factor, rG-CSF) is a hematopoietic growth factor which regulates the production and function of neutrophils. Filgrastim controls proliferation of committed progenitor cells and influences their maturation into mature neutrophils. Filgrastim also stimulates the release of neutrophils from bone marrow storage pools and reduces their maturation time. Filgrastim acts to increase the phagocytic activity of mature neutrophils. In patients receiving cytotoxic chemotherapy, filgrastim can accelerate neutrophil recovery, leading to a reduction in duration of the neutropenic phase.[1]

PHARMACOKINETICS:

Oral Absorption	no	
Distribution	not fully identified	
	cross blood brain barrier?	no information found
	volume of distribution	127-240 mL/kg
	plasma protein binding	no information found
Metabolism	not fully identified, however, the serum levels drop as the neutrophil count climbs, raising the possibility that the granulocytes are involved[1,3-7]; filgrastim binds to the G-CSF receptor on the neutrophil surface, creating a drug-receptor complex that is internalized to the endosomal compartments and either recycled or degraded[2]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	not fully identified; receptor mediated disposition[2]	
	urine	no information found
	feces	no information found
	terminal half life	1.3-7.2 hours
	clearance	0.31-0.71 mL/min/kg

Adapted from standard reference[1,3-7] unless specified otherwise.

USES:

Primary uses:

*Rescue of patients with febrile neutropenia

*Prevent neutropenia which interferes with potentially curative chemotherapy

*Stimulate engraftment post-BMT

Other uses:

Aplastic anemia

Augment peripheral blood stem cell harvest

Chronic benign cyclical neutropenia

Myelodysplastic syndrome

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to E. coli derived products, filgrastim, or pegfilgrastim.[8]

Caution:
- The safety and efficacy of filgrastim given ***simultaneously with cytotoxic chemotherapy*** has not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use filgrastim in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy.[8]
- The safety and efficacy of filgrastim given ***simultaneously with radiation therapy*** has not been evaluated; avoid concurrent therapy.[8]
- Filgrastim is a ***growth factor*** that primarily stimulates the production of neutrophils. However, the possibility that filgrastim can act as a growth factor for certain tumour types, particularly myeloid malignancies, cannot be excluded. Therefore, because of the possibility of tumour growth, use with caution in patients with myelodysplasia or in any malignancy with myeloid characteristics.[3,9]
- Because filgrastim can cause increased uric acid levels, patients who have a ***history of gout*** or malignancies that are known to be associated with ***increased uric acid levels***, should be monitored regularly.[3,9]
- ***Sickle cell crisis***, sometimes resulting in death, has been associated with filgrastim use in patients with sickle cell trait or sickle cell disease.[8]

Carcinogenicity: no information found

Mutagenicity: Filgrastim was not mutagenic in bacterial gene microsome tests.[8]

Fertility: Filgrastim had no observed effect on fertility in male or female test subjects in animal studies.[2]

Pregnancy: Animal data appears to be species dependent. Increased abortion and embryolethality were observed in treated rabbits. When administered during the period of organogenesis, filgrastim was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities, and decreased body weight, live births, and food consumption. External abnormalities were not observed in fetuses born to treated dams. In contrast, reproductive studies in rats showed no association with lethal, teratogenic, or behavioural effects on fetuses when administered during organogenesis. Offspring of treated dams exhibited a delay in external differentiation (e.g., detachment of auricles and descent of testes), slight growth retardation, and decreased body weights at birth with a slightly reduced survival rate.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	leukocytosis (dose related)
	sickle cell crisis[8] (<1%)
	splenic rupture[8] (<1%)
	splenomegaly (30%, with long term use)[8]; see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	thrombocytopenia (6-12%)[11]
cardiac	cardiac events, including myocardial infarctions and arrhythmias[8] (3%)
general disorders and administration site conditions	*extravasation hazard:* none[12]
	slight stinging on injection
immune system	hypersensitivity (<1%); see paragraph following **Side Effects** table
investigations	transient increase in LDH (27-58%)
	transient increase in LAP (27-58%)
	transient increase in uric acid (27-58%)
	hematuria/proteinuria (rare)
musculoskeletal and connective tissue	bone pain, transient (24%); see paragraph following **Side Effects** table
	osteoporosis (7% with long term use)[8]; see paragraph following **Side Effects** table
	pseudogout[8] (<1%)
respiratory, thoracic and mediastinal	acute respiratory distress syndrome[8] (<1%); see paragraph following **Side Effects** table
	alveolar hemorrhage[8] (<1%); manifesting as pulmonary infiltrates and hemoptysis
skin and subcutaneous tissue	alopecia (<1%)[11]
	cutaneous vasculitis[8] (<1%); see paragraph following **Side Effects** table
	exacerbation of pre-existing skin disorders, e.g., psoriasis (<1%)[11]
	Sweet's syndrome[8] (<1%)
vascular	capillary leak syndrome[8] (<1%); see paragraph following **Side Effects** table

Adapted from standard reference[3,6,9] unless specified otherwise.

Medullary ***bone pain***, reported in 24% of patients, was the only consistently observed adverse reaction attributed to filgrastim therapy. This bone pain was generally reported to be of mild-to-moderate severity and could be controlled in most patients with non-narcotic analgesics; infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20-100 mcg/kg/day) administered intravenously and less frequently in patients treated with lower subcutaneous doses of filgrastim (3-10 mcg/kg/day). This bone pain is thought to be the result of the marrow expansion that occurs from the increase in the neutrophil pool, which can cause a sensation of pressure or pain. Bone pain is transient (24-48 hours), tends to occur one to two days prior to the increase in circulating neutrophils and is most commonly observed in the sternum, pelvis, and/or lower back.[3,6,9]

Cases of ***capillary leak syndrome*** (CLS) have been reported in patients receiving filgrastim. CLS can cause circulatory shock and is characterized by hypotension, generalized edema, hypoalbuminemia, and hemoconcentration. Episodes can vary in frequency and severity and may be life-threatening if treatment is delayed. If CLS is suspected, filgrastim should be stopped and patients closely monitored.[10,13]

Hypersensitivity, including serious allergic reactions and anaphylaxis, has occurred during initial and subsequent treatments with filgrastim. Reactions are generally characterized by systemic symptoms, most often rash, urticaria, facial edema, wheezing, dyspnea, hypotension, and tachycardia. Reactions tend to occur within the first 30 minutes after administration, and appear more frequently with IV administration. Symptoms rapidly resolve in most patients

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after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Among patients who were rechallenged, symptoms recurred in more than half. Permanently discontinue filgrastim after serious reactions.[8]

Osteoporosis has been reported in approximately 7% of patients receiving filgrastim therapy for up to 4.5 years in clinical trials in patients with severe chronic neutropenia. Patients with underlying osteoporotic bone disease should be monitored for bone density changes while on long-term filgrastim therapy.[8]

Acute respiratory distress syndrome (ARDS) is reported in patients receiving filgrastim and is postulated to occur secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients who develop fever, lung infiltrates, or respiratory distress should be evaluated for ARDS and filgrastim should be withheld until resolution of symptoms or discontinued if necessary.[8]

In patients with severe chronic neutropenia receiving long-term filgrastim, subclinical ***splenomegaly*** (detected by CT or MRI scan) was reported as the most frequent adverse event. In adult patients this was observed to occur in approximately 33% of patients; 3% of patients were noted to have clinical splenomegaly.[3,6,9] Splenic rupture, including fatal cases, has been reported. Patients reporting left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.[8]

Cutaneous vasculitis has been reported, mostly in patients receiving long-term filgrastim therapy. In most cases, severity was rated as moderate or severe.[8] Common clinical features of vasculitis may include: petechiae, palpable purpura, hemorrhagic bullae, subcutaneous nodules, or ulceration.[14] Symptoms of vasculitis generally develop simultaneously with the increase in ANC and abate when the ANC decreases. Patients may be able to continue filgrastim at a reduced dose.[8] The reaction usually resolves spontaneously after discontinuation or filgrastim dose reduction; corticosteroids have been used for treatment of symptoms.[15]

INTERACTIONS: [16,17]

AGENT	EFFECT	MECHANISM	MANAGEMENT
myelosuppressive chemotherapy	decreased effectiveness of filgrastim	rapidly dividing myeloid cells (stimulated by filgrastim) may be destroyed by chemotherapy	do not administer concurrently; do not use filgrastim in the period 24 hours **before** administration of myelosuppressive chemotherapy through to 24 hours **after** the administration of myelosuppressive chemotherapy

SUPPLY AND STORAGE:

Biosimilar formulations of filgrastim are available.

***Injection*:**

Amgen Canada Inc. supplies filgrastim (NEUPOGEN®) as 1 mL and 1.6 mL single-use (preservative free) vials in a concentration of 300 mcg/mL AND 0.5 mL and 0.8 mL single-use (preservative free) prefilled syringes in a concentration of 600 mcg/mL. Refrigerate. Protect from light. Avoid vigorous shaking. The needle cover of the prefilled syringe contains natural rubber (a derivative of latex).[2]

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Apotex Inc. supplies filgrastim (GRASTOFIL®) as 0.5 mL and 0.8 mL single-use (preservative free) prefilled syringes in a concentration of 600 mcg/mL. Refrigerate. Protect from light. Avoid vigorous shaking. Prefilled syringe system contains natural rubber (a derivative of latex).[18]

Pfizer Canada ULC supplies filgrastim (NIVESTYM®) as 1 mL and 1.6 mL single-use (preservative free) vials in a concentration of 300 mcg/mL AND 0.5 mL and 0.8 mL single-use (preservative free) prefilled syringes in a concentration of 600 mcg/mL. Refrigerate. Protect from light. Avoid vigorous shaking.[19]

Tanvex BioPharma USA, Inc. supplies filgrastim (NYPOZI®) as 0.5 mL and 0.8 mL single-use (preservative free) prefilled syringes in a concentration of 600 mcg/mL. Refrigerate. Protect from light. Avoid vigorous shaking.[20]

Additional information:
Maximum single storage period at room temperature prior to use (by brand); discard if not used:
- NEUPOGEN®: 14 days[2]
- GRASTOFIL®: 15 days[18]
- NIVESTYM®: 15 days[19]
- NYPOZI®: 15 days[20]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- do NOT dilute with saline at any time; product may precipitate[2]
- the addition of albumin is recommended (at a concentration of 2 mg/mL) for filgrastim solutions diluted to 5-15 mcg/mL in 5% dextrose in order to prevent adsorption of the filgrastim to plastic[2]
- dilution to final concentrations less than 5 mcg/mL is not recommended, even in the presence of albumin[2]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:[1,2,23]

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	• ***preferred route*** • rotate sites • may be given as continuous SC infusion
Intramuscular	no information available on this route
Direct intravenous	not recommended
Intermittent infusion	• over 15-30 minutes • length of administration has been recommended at 2-4 hours to decrease bone pain • dilute solutions must have albumin added to prevent adsorption
Continuous infusion	dilute solutions must have albumin added to prevent adsorption
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found

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BC Cancer administration guideline noted in ***bold***, ***italics***

Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults and children*:**

BC Cancer usual dose noted in ***bold, italics***

Intravenous/subcutaneous[1,3,16,23]*:* ***5 mcg/kg or 200 mcg/m^2 SC*** or IV ***daily*** for up to 2 weeks or until the ANC reaches 1 x 10^9/L following the expected nadir. Treatment should be continued if the patient has clinical signs of infection, does not have a rising ANC, or is in a situation in which persistent marrow compromise is suspected.

May be increased by 5 mcg/kg each chemotherapy cycle depending on response. Discontinuation usually results in a 50% drop in circulating neutrophils within 1-2 days, with a return to pretreatment levels in 1-7 days. Therapy should be discontinued if the absolute neutrophil count (ANC) surpasses 10x10^9/L after the ANC nadir has occurred to avoid potential risks of excessive leukocytosis.

Dose can be rounded off to 300 or 480 mcg to avoid wastage.

Dosage in renal failure: no adjustment required

Dosage in hepatic failure: no adjustment required

Dosage in dialysis: no information found

REFERENCES:

1. Hollingshead LM, Goa K. Recombinant granulocyte colony-stimulating factor (rG-CSF): A review of its pharmacological properties and prospective role in neutropenic conditions. Drugs 1991;42:300-330
2. Amgen Canada Inc. NEUPOGEN® product monograph. Mississauga, Ontario; May 5 2023
3. Amgen (Canada) Inc. NEUPOGEN® product monograph. Mississauga, Ontario; February 1992
4. Yoshida T, Nakamura S, Ohtake S, et al. Effect of granulocyte colony-stimulating factor on neutropenia due to chemotherapy for non-Hodgkin's lymphoma. Cancer 1990;66(9):1904-1909
5. Stute N, Santana VM, Rodman JH, et al. Pharmacokinetics of subcutaneous recombinant human granulocyte colony- stimulating factor in children. Blood 1992;79(11):2849-2854
6. Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony- stimulating factor (first of two parts). N.Engl.J.Med. 1992;327(1):28-35
7. Miller LL. Current status of G-CSF in support of chemotherapy and radiotherapy. Oncology 1993;7(10):67-83
8. Amgen Canada Inc. NEUPOGEN® product monograph. MIssissauga, Ontario; March 21 2014
9. NEUPOGEN Product Review. Canadian Hospital Pharmacist. 1992;2:22-35
10. Amgen Inc. NEUPOGEN® product monograph. Thousand Oaks, California, USA; September 2013
11. Lexi-Drugs® (database on the Internet). Filgrastim. Lexi-Comp Inc., 2014. Available at: http://online.lexi.com. Accessed 7 July, 2014
12. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; March 1 2021

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13. Amgen Canada Inc. Health Canada Endorsed Important Safety Information on NEUPOGEN® and NEULASTA® - NEUPOGEN® (filgrastim) and NEULASTA® (pegfilgrastim) are associated with a risk of Capillary Leak Syndrome in patients with cancer and in healthy donors. Health Canada, 2012. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/
14. Fett N. Evaluation of adults with cutaneous lesions of vasculitis. In: 2014 UpToDate®; Basow,Denise S. (Ed); updated 10 March 2014; accessed 25 August 2014. Waltham, Massachusetts: UpToDate®; Available at www.uptodate.com; 2014
15. Jain KK. Cutaneous vasculitis associated with granulocyte colony-stimulating factor. J Am Acad Dermatol 1994;31(2 part 1):213-215
16. Krogh C. Compendium of pharmaceuticals and specialties 1993. 28th ed. Ottawa, Ontario: Canadian Pharmaceutical Association; 1993. p. 798-800
17. McEvoy GK, editor. AHFS 1993 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; . p. 863
18. Apotex Inc. GRASTOFIL® product monograph. Toronto, Ontario; August 4 2023
19. Pfizer Canada-ULC. NIVESTYM® product monograph. Kirkland, Québec; October 27 2023
20. Tanvex BioPharma USA Inc. NYPOZI® product monograph. Irvine, California, USA; October 8, 2021
21. Amgen Canada Inc. NEUPOGEN® product monograph. MIssissauga, Ontario; 31 October 2016
22. Apotex Inc. GRASTOFIL® product monograph. Toronto, Ontario; October 7 2016
23. Granulocyte colony-stimulating factors. Med Lett Drugs Ther 1991;33:61-63

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