DRUG NAME: Filgrastim

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

COMMON TRADE NAME(S): NEUPOGEN®, GRASTOFIL® (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	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	not fully identified	
	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[1-6] unless specified otherwise.

USES:

Primary uses:

*Rescue of febrile neutropenic patients

*Prevent neutropenia which interferes with potentially curative chemotherapy

*Stimulate engraftment post BMT

*Health Canada approved indication

Other uses:

Aplastic anemia

Augment peripheral blood stem cell harvest

Chronic benign cyclical neutropenia

Myelodysplastic syndrome

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to E. coli derived products, filgrastim, or pegfilgrastim.[7]

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.[7]
- The safety and efficacy of filgrastim given ***simultaneously with radiation therapy*** has not been evaluated; avoid concurrent therapy.[7]
- 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.[2,8]
- 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.[2,8]
- ***Sickle cell crisis***, sometimes resulting in death, has been associated with filgrastim use in patients with sickle cell trait or sickle cell disease.[7]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in bacterial gene microsome tests.[7]

Fertility: Filgrastim had no observed effect on fertility in males or females in animal studies.[7]

Pregnancy: FDA Pregnancy Category C.[9] Animal studies have shown fetal risk and there are no controlled studies in women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. In animal studies, increased abortion and embryolethality were observed as well as genitourinary bleeding, developmental abnormalities, decreased body weight at birth, and reduced food consumption.[7]

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[7] (<1%)
	splenic rupture[7] (<1%)
	splenomegaly (30%, with long term use)[7]; see paragraph following **Side Effects** table
	thrombocytopenia (6-12%)[10]
cardiac	cardiac events, including myocardial infarctions and arrhythmias[7] (3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders and administration site conditions	*extravasation hazard: none*[11]
	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)[7]; see paragraph following **Side Effects** table
	pseudogout[7] (<1%)
respiratory, thoracic and mediastinal	acute respiratory distress syndrome[7] (<1%); see paragraph following **Side Effects** table
	alveolar hemorrhage[7] (<1%); manifesting as pulmonary infiltrates and hemoptysis
skin and subcutaneous tissue	alopecia (<1%)[10]
	cutaneous vasculitis[7] (<1%); see paragraph following **Side Effects** table
	exacerbation of pre-existing skin disorders, e.g., psoriasis (<1%)[10]
	Sweet's syndrome[7] (<1%)
vascular	capillary leak syndrome[7] (<1%); see paragraph following **Side Effects** table

Adapted from standard reference[2,5,8] 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.[2,5,8]

Cases of ***capillary leak syndrome*** (CLS) have been reported in patients receiving filgrastim. CLS can cause circulatory shock and 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.[9,12]

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 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.[7]

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.[7]

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.[7]

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.[2,5,8] 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.[7]

Cutaneous vasculitis has been reported, mostly in patients receiving long-term filgrastim therapy. In most cases, severity was rated as moderate or severe.[7] Common clinical features of vasculitis may include: petechiae, palpable purpura, hemorrhagic bullae, subcutaneous nodules, or ulceration.[13] 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.[7] The reaction usually resolves spontaneously after discontinuation or filgrastim dose reduction; corticosteroids have been used for treatment of symptoms.[14]

INTERACTIONS: [15,16]

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 vials of preservative free solution 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).[17]

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]

Additional information:
NEUPOGEN®:
- vials and prefilled syringes may be kept at room temperature for a maximum of 14 days prior to use[19]

GRASTOFIL®:
- prefilled syringes may be kept at room temperature for a maximum of 15 days prior to use[18]

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[7]
- 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[7]
- dilution to final concentrations less than 5 mcg/mL is not recommended, even in the presence of albumin[7]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:[1,2,20]

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	• in D5W (not NS) over 15-30 minutes either once daily or q12h. • length of administration has been recommended at 2-4 hours to decrease bone pain. • dilute solutions must have albumin added.
Continuous infusion	dilute solutions must have albumin added
Intraperitoneal	no information available on this route
Intrapleural	no information available on this route
Intrathecal	no information available on this route
Intra-arterial	no information available on this route
Intravesical	no information available on this route

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults and children*:**

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

Intravenous/subcutaneous[1,2,15,20]*:* ***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.

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

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

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