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.

PHARMACOKINETICS:

<table>
<thead>
<tr>
<th>Oral Absorption</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>not fully identified</td>
</tr>
<tr>
<td>cross blood brain barrier?</td>
<td>no information found</td>
</tr>
<tr>
<td>volume of distribution</td>
<td>127-240 mL/kg</td>
</tr>
<tr>
<td>plasma protein binding</td>
<td>no information found</td>
</tr>
<tr>
<td>Metabolism</td>
<td>not fully identified, however, the serum levels drop as the neutrophil count climbs, raising the possibility that the granulocytes are involved</td>
</tr>
<tr>
<td>active metabolite(s)</td>
<td>no information found</td>
</tr>
<tr>
<td>inactive metabolite(s)</td>
<td>no information found</td>
</tr>
<tr>
<td>Excretion</td>
<td>not fully identified</td>
</tr>
<tr>
<td>urine</td>
<td>no information found</td>
</tr>
<tr>
<td>feces</td>
<td>no information found</td>
</tr>
<tr>
<td>terminal half life</td>
<td>1.3-7.2 hours</td>
</tr>
<tr>
<td>clearance</td>
<td>0.31-0.71 mL/min/kg</td>
</tr>
</tbody>
</table>

Adapted from standard reference 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.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood and lymphatic system/ febrile</td>
<td>leukocytosis (dose related)</td>
</tr>
<tr>
<td>neutropenia</td>
<td>sickle cell crisis(^7) (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>splenic rupture(^7) (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>splenomegaly (30%, with long term use)(^7); see paragraph following Side Effects table</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia (6-12%)(^10)</td>
</tr>
<tr>
<td>cardiac</td>
<td>cardiac events, including myocardial infarctions and arrhythmias(^7) (3%)</td>
</tr>
</tbody>
</table>
### ORGAN SITE | SIDE EFFECT
--- | ---
**general disorders and administration site conditions** | extravasation hazard: none
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); see paragraph following Side Effects table
pseudogout (<1%)

**respiratory, thoracic, and mediastinal** | acute respiratory distress syndrome (<1%); see paragraph following Side Effects table
alveolar hemorrhage (<1%); manifesting as pulmonary infiltrates and hemoptysis

**skin and subcutaneous tissue** | alopecia (<1%)
cutaneous vasculitis (<1%); see paragraph following Side Effects table
exacerbation of pre-existing skin disorders, e.g., psoriasis (<1%)
Sweet’s syndrome (<1%)

**vascular** | capillary leak syndrome (<1%); see paragraph following Side Effects table

Clinically important side effects are in **bold, italics**.

Adapted from standard reference unless specified otherwise.

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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.

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, hypoalbuninemia, 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.

**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.

**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.
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                                                                                     |
|----------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------ handwriting
| 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 use¹⁹

GRASTOFIL®:
- prefilled syringes may be kept at room temperature for a maximum of 15 days prior to use¹⁸
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
- 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
- dilution to final concentrations less than 5 mcg/mL is not recommended, even in the presence of albumin

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:1,2,20

<table>
<thead>
<tr>
<th>Route</th>
<th>BC Cancer administration guideline noted in bold, italics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous</td>
<td>• preferred route</td>
</tr>
<tr>
<td></td>
<td>• rotate sites</td>
</tr>
<tr>
<td></td>
<td>• may be given as continuous SC infusion</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>no information available on this route</td>
</tr>
<tr>
<td>Direct intravenous</td>
<td>not recommended</td>
</tr>
<tr>
<td>Intermittent infusion</td>
<td>• in D5W (not NS) over 15-30 minutes either once daily or q12h.</td>
</tr>
<tr>
<td></td>
<td>• length of administration has been recommended at 2-4 hours to decrease bone pain.</td>
</tr>
<tr>
<td></td>
<td>• dilute solutions must have albumin added.</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>dilute solutions must have albumin added</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>no information available on this route</td>
</tr>
<tr>
<td>Intrapleural</td>
<td>no information available on this route</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>no information available on this route</td>
</tr>
<tr>
<td>Intra-arterial</td>
<td>no information available on this route</td>
</tr>
<tr>
<td>Intravesical</td>
<td>no information available on this route</td>
</tr>
</tbody>
</table>

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults and children:

Intravenous/subcutaneous1,2,15,20, 5 mcg/kg or 200 mcg/m² SC or IV daily for up to 2 weeks or until the ANC reaches 1 x 10⁹/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.
Filgrastim

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 10x10⁹/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: