

DRUG NAME: Filgrastim**SYNONYM(S):** Granulocyte colony stimulating factor (G-CSF)**COMMON TRADE NAME(S):** NEUPOGEN®**CLASSIFICATION:** miscellaneous*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**¹

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:¹⁻⁶

Oral Absorption	no	
Distribution	not fully identified	
	cross blood brain barrier?	no information found
	Vd	127-240 mL/kg
	PPB	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
	t _{1/2}	1.3-7.2 hours
	Cl	0.31-0.71 mL/min/kg

USES:^{1,7}

- * Rescue of febrile neutropenic patients
- * Prevent neutropenia which interferes with potentially curative chemotherapy
- * Stimulate engraftment post BMT

- * Health Protection Branch approved indication.

Less frequent uses include:
 Aplastic anemia
 Augment peripheral blood stem cell harvest
 Chronic benign cyclical neutropenia
 Myelodysplastic syndrome

SPECIAL PRECAUTIONS:^{2,8}

Filgrastim is **contraindicated** in patients with known hypersensitivity to E. coli derived products or to any constituent of the product.

The safety and efficacy of **filgrastim given simultaneously with cytotoxic chemotherapy** have 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.

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.

The **carcinogenic potential** of filgrastim has not been studied. Its safe use in **pregnancy** and its effects on **fertility** have not been established. **Breast feeding** is not recommended due to the potential secretion into breast milk.

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.

SIDE EFFECTS:^{2,5,8}

ORGAN SITE	SIDE EFFECT	ONSET			
dermatologic	exacerbation of pre-existing skin disorders eg, psoriasis (rare)		E		
	alopecia (rare)		E		
hematologic	leukocytosis (dose related)		E		
	thrombocytopenia (rare)		E		
	splenomegaly (3%, with long term use)		E		
hypersensitivity	Type I (anaphylactoid, <0.01%)	I			
injection site	slight stinging on injection	I			
musculoskeletal	transient bone pain (24%)		E		
	osteoporosis (2% with long term use)			D	

ORGAN SITE	SIDE EFFECT	ONSET			
renal/metabolic	transient increase in LDH (27-58%)		E		
	transient increase in LAP (27-58%)		E		
	transient increase in uric acid (27-58%)		E		
	hematuria/proteinuria (rare)		E		

Dose-limiting side effects are underlined.

I = immediate (onset in hours to days); E = early (days to weeks);

D = delayed (weeks to months); L = late (months to years)

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.

Osteoporosis has been reported in less than 2% of patients receiving filgrastim therapy for up to two years in clinical trials in patients with severe chronic neutropenia.

There have been rare reports of symptoms suggestive of **allergic-type reactions** but in which an immune component has not been demonstrated. Symptoms have included dyspnea/wheezing, hypotension/syncope and urticaria/facial edema. These reactions occurred more frequently with IV administration. Approximately one-third of the patients were rechallenged, with recurrence of symptoms.

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**.

INTERACTIONS:^{7,9}

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 through 24 hours after the administration of myelosuppressive chemotherapy

SOLUTION PREPARATION AND COMPATIBILITY:^{2,7,10}

Injection: 300 mcg/mL clear, colourless liquid in 1 mL (300 mcg) and 1.6 mL (480 mcg) vials; preservative-free; contains sodium acetate as a buffer, 0.004% Tween 80 and mannitol 50 mg per mL. Store in refrigerator (2-8°C). May be allowed to reach room temperature for up to 24 hours. Freezing or storage at temperatures greater than 30°C results in aggregate formation and solutions stored under such conditions should not be used. Avoid vigorous shaking. Discard unused portions of vials and vials left at room temperature for more than 24 hours.

Diluted solution for infusion: Incompatible with NS. When administering filgrastim through IV lines that have been used to infuse saline, the lines should be flushed with D5W before and after filgrastim administration. Compatible with D5W in PVC, polyolefin and propylene containers. For dilutions below 15 mcg/mL, albumin to a final concentration of 2 mg/mL or more must first be added to the D5W to prevent adsorption of filgrastim to the infusion container walls. Filgrastim should not be diluted to less than 5 mcg/mL even in the presence of albumin.¹¹ Dilutions in D5W, with or without albumin, are physically stable for up to 7 days refrigerated (2-8°C) or at room temperature below 30°C. However, because the solution contains no preservative, the manufacturer recommends using dilutions within 24 hours.

Stability in syringes: Undiluted filgrastim in Becton-Dickinson tuberculin syringes is physically stable for 7 days refrigerated (2-8°C) or 24 hours at room temperature below 30°C. However, because the solution contains no preservative, the manufacturer recommends that prefilled syringes be refrigerated and used within 24 hours.

It is recommended that filgrastim **not be mixed with other drugs. Incompatible** with saline solution.

PARENTERAL ADMINISTRATION:^{1,2,12}

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:^{1,2,7,12}

Refer to protocol by which patient is being treated.

Adults and children:

IV/SC:

daily: 5 mcg/kg or 200 mcg/m² 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.

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

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