# Myeloid Cytokines (Growth Factors, Colony-stimulating Factors) for Radiation-induced Myelosuppression

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Adult Dose</th>
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<tr>
<td>G-CSF: filgrastim (Neupogen®)</td>
<td>• Subcutaneous administration&lt;br&gt;• 10 mcg/kg/day via single daily injection in adults and children&lt;br&gt;• Continue until absolute neutrophil count remains greater than 1,000/mm³ ( = 1.0 x 10⁹ cells/L) for 3 consecutive (daily) CBCs or exceeds 10,000/mm³ ( = 10 x 10⁹ cells/L) after a radiation-induced nadir.&lt;br&gt;• Of the 5 myeloid cytokines listed on this page, only Neupogen® is FDA-approved for treatment of radiation-induced myelosuppression.&lt;br&gt;• <a href="#">See below for details</a></td>
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<tr>
<td>Pegylated G-CSF: pegfilgrastim (Neulasta®)</td>
<td>• 1 subcutaneous dose, 6 mg&lt;br&gt;• Consider second 6 mg dose 7 or more days after initial dose, if significant neutropenia persists</td>
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<tr>
<td>GM-CSF: sargramostim (Leukine®)</td>
<td>• Subcutaneous administration&lt;br&gt;• 250 mcg/m²/day&lt;br&gt;• Continued until absolute neutrophil count &gt; 1,000/mm³ ( = 1.0 x 10⁹ cells/L)</td>
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G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor.

Recently developed granulocyte colony-stimulating factors (G-CSFs)

- **Neither is FDA-approved for radiation-induced myelosuppression.**
  - **tbo-filgrastim (Granix®) (Teva)**
    - Was approved initially for clinical use in the US by the [FDA in August 2012](https://www.fda.gov/Drugs/ApprovalInformation/DrugsApproved/ucm280139.htm).
    - Drug labeling was updated to reflect licensing for [self-administration by patients and caregivers in December 2014](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/175899s023lbl.pdf).
    - [Drug label for tbo-filgrastim](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/175899s023lbl.pdf) (PDF - 1.6 MB)
  - **filgrastim-sndz (Zarxio™) (Sandoz/Novartis)**
    - FDA approved filgrastim-sndz (ZARXIO™ Injection, Sandoz Inc.), as biosimilar to US-licensed Neupogen® on March 6, 2015. The date for drug availability in the US has not yet been announced.
    - It was approved for the five indications, but not for radiation-induced myelosuppression (see label).
- The formulation of ZARXIO™ differs from that of US-licensed Neupogen® in one inactive component.
- [Drug label for filgrastim-sndz](PDF - 2.9 MB)

**General comments:**

- This class of drugs is referred to by various names.
  - Myeloid, white cell, or leukocyte cytokines
  - Myeloid, white cell, or leukocyte growth factors
  - Myeloid, white cell, or leukocyte colony-stimulating factors (CSFs)
- Specific individual drugs in this class target specific kinds of myeloid cell(s).
  - Neutrophil only (granulocyte-G) only (e.g., filgrastim, a G-CSF)
  - Neutrophil and monocytes/macrophages and myeloid-derived dendritic cells (e.g. sargramostim, a GM-CSF)
- Listing on this page does NOT mean that each product is in the [U.S. Strategic National Stockpile (SNS)](Link).
- Consult hyperlinks in the first column of the table for important drug information.
- See REMM [Exposure Algorithm](Link) for the clinical context for using these drugs to treat radiation-induced myelosuppression in the context of the Acute Radiation Syndrome.

**Key Clinical Information**

- The goals of using a myeloid colony-stimulating factor for radiation-induced myelosuppression
  - Shorten the duration of severe neutropenia
  - Minimize the severity of neutropenia-associated complications, including infection
  - Improve survival of adults and children exposed to myelosuppressive doses of radiation.
- Initiation of treatment in a radiation incident should be strongly considered for patients who
  - Are likely to have received ≥2 Gy whole body exposure or ≥2 Gy significant partial body exposure
  - Are likely to develop an absolute neutrophil count of 500 cells/mm³
  - Will likely have prolonged periods of significant neutropenia ([See diagram](Link)).
  - Have significant radiation exposure plus trauma and/or burns, which worsens the clinical outcome compared to radiation exposure alone.
• REMM provides various interactive biodosimetry tools to help estimate the dose of whole body radiation received.

• As of March 2015, of the 5 myeloid cytokines listed on this page, only Neupogen® has been FDA-approved for the indication of radiation-induced myelosuppression.

• Consult REMM’s Interactive Scarce Resources Tool to assist with patient triage and allocation of scarce resources including these cytokines in the first 96 hours of a mass casualty incident such as detonation of an Improvised Nuclear Device (IND).

• Administration of myeloid cytokine is recommended as early as possible after expected or confirmed exposure to radiation, and usually within 24 hours after the end of radiation exposure.

**FDA guidance**

• Approval of Neupogen® for radiation-induced myelosuppression was based on FDA’s "Animal Rule".

• See the Neupogen® drug label update from March 2015 for details about approval for this indication.

• How and when to consider Neupogen® to treat myelosuppression from radiation exposure
  
  o The recommended dose of Neupogen® is 10 mcg/kg as a single daily subcutaneous injection for adult and pediatric patients exposed to myelosuppressive doses of radiation.

  o Administer Neupogen® as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).

  o Estimate a patient's absorbed radiation dose based on
    ▪ Information from public health authorities (e.g., dose reconstruction)
    ▪ Biodosimetry, if available
    ▪ Clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

  o Obtain a baseline complete blood count (CBC) and then serial CBCs approximately every third day until the absolute neutrophil count (ANC) remains greater than 1,000/mm³ (= 1.0 x 10⁹ cells/L) for 3 consecutive CBCs. *(REMM Note: More frequent CBCs, including daily CBCs, are likely to be ordered if laboratory resources permit.)*

  o **Do not delay administration of Neupogen® if a CBC is not readily available.**
• Continue administration of Neupogen® until the absolute neutrophil count (ANC) remains
  ▪ Greater than 1,000/mm³ (= 1.0 x 10⁹ cells/L) for 3 consecutive CBCs or
  ▪ Exceeds 10,000/mm³ (= 10 x 10⁹ cells/L) after a radiation-induced nadir
  ▪ REMM Note: CBCs with the target ANC level on 3 consecutive days is also acceptable as a stopping point for drug administration.

• How the daily dose was selected
  o Because of the uncertainty associated with extrapolating animal efficacy data to humans, the selection of human dose for Neupogen® is aimed at providing exposures to filgrastim that exceed those observed in animal efficacy studies.
  o The 10 mcg/kg daily dose is selected for humans exposed to myelosuppressive doses of radiation because the exposure associated with such a dose is expected to exceed the exposure associated with a 10 mcg/kg dose in non-human primates.
  o The safety of Neupogen® at a daily dose of 10 mcg/kg has been assessed on the basis of clinical experience in other approved indications.

• Ethics of using Neupogen®: comments from the drug label
  o No prospective randomized human clinical trials have proven either the efficacy or long-term safety of myeloid growth factors for radiation-induced myelosuppression in humans.
  o Efficacy studies of Neupogen® could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons.
  o Approval of this indication was based on efficacy studies conducted in animals and data supporting the use of Neupogen® for other approved indications.
  o Clinicians should advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) that efficacy studies of Neupogen® for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals.
  o (REMM Note: Considerable clinical experience has been gained worldwide using myeloid cytokines to treat patients after accidental radiation exposure.)

**Procuring and using myeloid cytokines during large mass casualty incidents**

• Neupogen®, which has been FDA-approved for the indication of radiation-induced myelosuppression, would not require an EUA, if used as advised on the drug label.
Obtaining and using most myeloid cytokines for radiation-induced myelosuppression from the Strategic National Stockpile would require a formal FDA Emergency Use Authorization (EUA).

In a very large mass casualty incident such as a nuclear detonation, off-label use of these cytokines by individual clinicians might occur from sources outside the SNS. Senior medical incident managers will probably provide guidance on this issue.

If there are significant shortages of resources, including myeloid cytokines, modification of standard dosing schedules may be recommended by senior medical incident managers for drug not stored in the SNS and/or by FDA's Emergency Use Authorization or Emergency Use Instruction for the supply of drug in the SNS.

If resources are scarce, including cytokines, triage modification including when to use cytokines may be considered in order to provide the greatest good for the greatest number.

Key safety issues for myeloid cytokines

- For each drug noted on this page, consult the FDA drug label for information about side effects.
- For radiation-induced myelosuppression in pregnant women
  - Experts in biodosimetry should be consulted.
  - Any pregnant patient with exposure to radiation should be evaluated by a health physical and maternal-fetal specialist for an assessment of risk to the fetus.
  - Class C refers to U.S. Food and Drug Administration Pregnancy Category C, which indicates that studies have shown animal, teratogenic, or embryocidal effects, but there are no adequate controlled studies in women; or no studies are available in animals or pregnant women.
  - Advise females of reproductive potential that Neupogen® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
- Pediatric Use
  - Use of Neupogen® to increase survival in patients acutely exposed to myelosuppressive doses of radiation is based on studies conducted in animals and clinical data supporting the use of Neupogen® in other approved indications.
  - The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adult patients receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim.
  - The pediatric dose is the same as the adult dose: 10 mcg/kg/day.
• **Warning and Precautions** on the drug label for each of the products in this category should be noted. Below is a list of serious adverse effects note on the Neupogen® drug label. Most are rare.
  
  o Splenic enlargement and rupture
  o Acute Respiratory Distress Syndrome
  o Serious allergic reactions
  o Sickle cell disorders: Sickle cell crisis, in some cases fatal, has been reported with the use of Neupogen® in patients with sickle cell trait or sickle cell disease.
  o Alveolar hemorrhage and hemoptysis
  o Capillary leak syndrome
  o Thrombocytopenia and Leukocytosis

**Clinical Practice Guidelines for Myeloid Cytokines**


• [Myeloid Growth Factors, National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology: Myeloid Growth Factors 2009](requires registration). See section entitled "NCCN Guidelines for Supportive Care".

• [American Society of Clinical Oncology](2006)

• Myeloid Growth Factors, NCCN Guidelines Version 2.2014, 5/2/2014, Registration on the [NCCN.org](web site required to access this guideline. It is listed under "Guidelines for supportive care". Extensive oncology bibliography is included.)