

Myeloid Cytokines for Acute Exposure to Myelosuppressive Doses of Radiation (Hematopoietic Subsyndrome of ARS)

Cytokine	Key Information
<p style="text-align: center;">G-CSF: filgrastim (Neupogen® drug label)</p>	<ul style="list-style-type: none"> • Administer 10 mcg/kg/day as a single daily subcutaneous injection in adults and children for the FDA-approved indication of acute exposure to myelosuppressive doses of radiation. • Continue daily administration 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. • See comments below this table about possible dosing changes for prescribing this drug during large mass casualty incidents when resources may be scarce. • Administer Neupogen® as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy). • Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics. • If possible, obtain a baseline complete blood count (CBC) prior to administration of first dose and then serial CBCs about every third day until the absolute neutrophil count (ANC) remains greater than 1,000/mm³ (= 1 x 10⁹ cells/L) for 3 consecutive CBCs. • Do NOT delay administration of Neupogen® if a CBC is not readily available. • See FDA-approved drug label for full prescribing information.
<p style="text-align: center;">Pegylated G-CSF: pegfilgrastim (Neulasta® drug label)</p>	<ul style="list-style-type: none"> • In adults, two doses, 6 mg each, administered subcutaneously one week apart for the FDA-approved indication of acute exposure to myelosuppressive doses of radiation. • In pediatric patients weighing less than 45 kg, refer to table in Neulasta drug label for dose calculated by weight. Administer two doses of drug subcutaneously one week apart. • See comments below this table about possible dosing changes for prescribing this drug during large mass casualty incidents when resources may be scarce. • Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). • Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available or clinical

	<p>findings such as time to onset of vomiting or lymphocyte depletion kinetics.</p> <ul style="list-style-type: none"> • If possible, obtain a baseline complete blood count (CBC) prior to administration of the first dose. • Do NOT delay the first dose of Neulasta® if a CBC is not readily available. • A CBC should be obtained prior to administration of the second dose of Neulasta®. Subject matter experts recommend not administering the second dose if absolute neutrophil count is greater than 5,000/mm³ (= 5.0 x 10⁹ cells/L). • See drug label for specific recommendations about how the prefilled syringe with 0.6 mL (6 mg) should be used, especially since doses of less than 6 mg are recommended for children weighing less than 45 kg. • See FDA-approved drug label for full prescribing information.
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G-CSF = granulocyte colony-stimulating factor

Other myeloid colony-stimulating factors (G-CSFs, GM-CSFs)

- The drugs below are in clinical use for various indications but are **NOT approved by the FDA for the specific indication of acute exposure to myelosuppressive doses of radiation.**
 - **sargramostim (Leukine®)** (Sanofi)
 - Granulocyte-macrophage colony-stimulating factor (GM-CSF)
 - [Drug label for sargramostim](#) (PDF - 150 KB)
 - **tbo-filgrastim (Granix®)** (Teva)
 - Granulocyte colony-stimulating factor (G-CSF)
 - Was approved initially for clinical use in the US by the [FDA in August 2012](#).
 - Drug labeling was updated to reflect licensing for [self-administration by patients and caregivers in December 2014](#).
 - [Drug label for tbo-filgrastim](#) (PDF - 1.6 MB)
 - **filgrastim-sndz (Zarxio™)** (Sandoz/Novartis)
 - Granulocyte colony-stimulating factor (G-CSF)
 - 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.
 - 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).

- Neutrophils only (e.g., filgrastim, a G-CSF)
 - Neutrophils and macrophages (e.g. sargramostim, a GM-CSF)
- Listing on this page does NOT mean that each product is in the [U.S. Strategic National Stockpile \(SNS\)](#).
- See [REMM Exposure Algorithm](#) for the clinical context for using these drugs to treat acute exposure to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of ARS).

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 have an absolute neutrophil count of 500 cells/mm³ or less
 - Will likely have prolonged periods of significant neutropenia ([See diagram](#)).
 - 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.
 - 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).
 - Two FDA-approved countermeasures for the indication of acute exposure to myelosuppressive doses of radiation
 - In March 2015, [Neupogen was FDA-approved for the indication acute exposure of radiation-induced myelosuppression](#).
 - In November 2015, [Neulasta was FDA-approved for the indication of acute exposure to radiation-induced myelosuppression](#).
- Approval of Neupogen[®] and Neulasta[®] for acute exposure to myelosuppressive doses of radiation was based on FDA's "[Animal Rule](#)".
- Ethics of using myeloid cytokines for treatment of acute exposure to myelosuppressive doses of radiation
 - No prospective randomized **human** clinical trials have proven either the efficacy or long- term safety of myeloid growth factors for acute exposure to myelosuppressive doses of radiation
 - Efficacy studies of these drugs could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons.
 - Approval of this indication was based on efficacy studies conducted **in animals** and data supporting the use of these drugs for other approved indications.
 - Clinicians should advise patients acutely exposed to myelosuppressive doses of radiation (at risk for the Hematopoietic Subsyndrome of ARS) that efficacy studies of these drugs 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](#).

- (REMM Note: Considerable clinical experience has been gained worldwide using myeloid cytokines to treat patients after accidental radiation exposure and for various other indications noted on the drug labels.)

Procuring and using myeloid cytokines during large mass casualty incidents

- Because both Neupogen® and Neulasta® are FDA-approved for the indication of acute exposure to myelosuppressive doses of radiation, neither would require an [Emergency Use Authorization \(EUA\)](#), if used as advised on the drug label for this indication.
- If there are **very significant shortages** of medical countermeasures, including myeloid cytokines, **senior medical incident managers may recommend modification of standard dosing schedules**.
 - **Neupogen®**: Senior managers might, for example, recommend using Neupogen® at a dose of 5 mcg/kg/day instead of 10 mcg/kg/day, dosing perhaps less frequently than daily until adequate supplies arrive to treat all patients at the higher daily dose, and/or stopping administration when ANC reaches 5,000/mm³ (= 5.0 x 10⁹ cells/L) rather than 10,000/mm³ (= 10.0 x 10⁹ cells/L). These recommendations, however, are NOT included in the FDA drug label.
 - **Neulasta®**: Senior managers might recommend giving the first dose of Neulasta® (day 1), and require a CBC prior to the second dose (day 8) in order to consider whether the second dose is necessary or possibly delay it. Subject matter experts would recommend NOT administering the second dose if the ANC exceeds 5,000/mm³ (= 5.0 x 10⁹ cells/L). These recommendations, however, are NOT included in the FDA drug label.
- [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 of people.](#)

Key safety issues for myeloid cytokines

- For each drug noted on this page, consult the FDA drug label for detailed information about side effects.
- **Pregnant women:** for use of these drugs for acute exposure to myelosuppressive dose of radiation in **pregnant women**
 - Experts in biodosimetry should be consulted.
 - Any pregnant patient with exposure to radiation should be evaluated by a health physicist and maternal-fetal specialist for an assessment of risk to the fetus.
 - **Both Neulasta® and Neupogen® are [FDA Pregnancy Category C drugs](#).**
 - This means **Risk not ruled out**: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
 - Advise females of reproductive potential that Neupogen® or Neulasta® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- **Warning and Precautions** on the drug label for each product in this category should be noted. Below is a list of serious adverse effects noted on the drug labels. Most are rare. Consult drug labels for more detailed information.
 - Splenic enlargement and rupture
 - Acute Respiratory Distress Syndrome
 - Serious allergic reactions
 - Sickle cell crisis
 - Alveolar hemorrhage and hemoptysis
 - Capillary leak syndrome
 - Thrombocytopenia and Leukocytosis
 - Note: bone pain, which occurs in approximately 25% of patients, is an adverse reaction, but it is not considered "serious".

Clinical Practice Guidelines for Myeloid Cytokines

- Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. [Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update](#). (2015 ASCO guideline) J Clin Oncol. 2015 Oct 1;33(28):3199-212. [PubMed Citation] (This 2015 ASCO guideline updates the [2006 myeloid cytokine guideline](#))
- [NCCN Clinical Practice Guidelines in Oncology, Myeloid Growth Factors, Version 1.2015](#). See section entitled "NCCN Guidelines for Supportive Care" > "Myeloid Growth Factors". (Registration required.)
- Dainiak N, Gent RN, et al. [First Global Consensus for Evidence-Based Management of the Hematopoietic Syndrome Resulting From Exposure to Ionizing Radiation](#). Disaster Med Public Health Prep. 2011 Oct;5(3):202-212. [PubMed Citation] ([Full text](#))

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