

Myeloid Cytokines for 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 are to:
 - 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.

Cytokine	Key Information
<p style="text-align: center;">G-CSF: filgrastim (Neupogen® drug label)</p>	<ul style="list-style-type: none"> • 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. • Administer Neupogen® as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy). Do NOT delay administration of Neupogen® if a CBC is not readily available. • Standard dosing - <ul style="list-style-type: none"> ○ Administer 10 mcg/kg/day (rounded to nearest vial size) as a single daily subcutaneous injection in adults and children for the FDA-approved indication of acute exposure to myelosuppressive doses of radiation.

	<ul style="list-style-type: none"> ○ 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. ○ Vial sizes are 300 mcg and 480 mcg. For a 70kg person, 2 vials of either size would be the appropriate dose. It would be reasonable to indicate a maximum dose like 960mcg OR two vials per dose though this is not uniformly agreed upon. Note that 2 injection sites would be required per dose. ○ See FDA-approved drug label for full prescribing information. ● Limited resource dosing - The AHRQ standard starting dose for children is 5 mcg/kg (CHOP uses the same starting dose) which is then titrated for effect as needed. In a potentially resource-restricted environment the lower dose could be initiated. 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. ● Lab monitoring - 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.
<p style="text-align: center;">Pegylated G-CSF: pegfilgrastim (Neulasta® drug label)</p>	<ul style="list-style-type: none"> ● 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. ● Administer Neulasta® - the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Do NOT delay the first dose of Neulasta® if a CBC is not readily available. ● Standard dosing - <ul style="list-style-type: none"> ○ In adults and children weighing ≥45 kg, 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.

	<p>Administer two doses of drug subcutaneously one week apart.</p> <ul style="list-style-type: none"> ○ 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. ● Limited resource dosing - 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. ● Lab monitoring - If possible, obtain a baseline complete blood count (CBC) prior to administration of the first dose. 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).
<p>GM-CSF: sargramostim (Leukine® drug label)</p>	<ul style="list-style-type: none"> ● 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. ● Administer Leukine® as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy). ● Standard dosing - For patients with hematopoietic syndrome of acute radiation syndrome (H-ARS), the recommended dose of Leukine is a subcutaneous injection administered once daily as follows: <ul style="list-style-type: none"> ○ 7 mcg/kg in adult and pediatric patients weighing greater than 40 kg ○ 10 mcg/kg in pediatric patients weighing 15 kg to 40 kg ○ 12 mcg/kg in pediatric patients weighing less than 15 kg ○ Continue administration of Leukine until absolute neutrophil count 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. ○ See FDA-approved drug label for full prescribing information. ● Lab monitoring - Obtain a baseline CBC with differential and then serial CBCs approximately every third day until the ANC remains

greater than 1,000/mm³ for three consecutive CBCs. Do not delay administration of Leukine if a CBC is not readily available.

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.**
 - **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 formulation of ZARXIO™ differs from that of US-licensed Neupogen® in one inactive component.
 - [Drug label for filgrastim-sndz](#) (PDF - 2.9 MB)
 - As of 2016, this drug is licensed for chemotherapy induced myelosuppression but not radiation induced myelosuppression.

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).
- 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).
 - Myeloid cytokines approved by the FDA for the indication of acute exposure to myelosuppressive doses of radiation:
 - Three myeloid cytokines (Neupogen®, Neulasta®, and Leukine®) are currently FDA-approved for the indication of acute exposure to myelosuppressive doses of radiation and therefore, would not require an [Emergency Use Authorization \(EUA\)](#), if used as advised on the drug label for this indication.
 - 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](#).
 - In March 2018, [Leukine was FDA-approved for the indication of acute exposure of radiation-induced myelosuppression](#).
 - Myeloid cytokines in the [Strategic National Stockpile \(SNS\)](#)
 - The first myeloid cytokines included in the SNS were Neupogen® and Leukine®.
 - On September 30, 2016 [HHS/ASPR/BARDA](#) purchased doses of myeloid cytokines (Neulasta® and Leukine®) for the US [Strategic National Stockpile \(SNS\)](#). These will supplement already existing SNS stores of Neupogen®.
 - See [HHS announcement](#)
 - See [ASPR announcement](#)
- Approval of Neupogen®, Neulasta®, and Leukine® for acute exposure to myelosuppressive doses of radiation was based on FDA's "[Animal Rule](#)".

- 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

- Neupogen®, Neulasta®, and Leukine® are FDA-approved for the indication of acute exposure to myelosuppressive doses of radiation and, therefore, would not 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.
 - **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[®], Neulasta[®], or Leukine[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Both Leukine injection (solution) and Leukine for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP contain benzyl alcohol, which has been associated with gasping syndrome in neonates and infants. The preservative benzyl alcohol can cause serious adverse reactions and death when administered intravenously to neonates and infants. If LEUKINE is needed during pregnancy, use only LEUKINE for injection (lyophilized powder) reconstituted with Sterile Water for injection without preservatives.
- **Lactation**
 - Risk Summary for Neupogen
 - Granulocyte colony-stimulating factor (G-CSF) is a normal component of breastmilk. However, the excretion of exogenous filgrastim in breastmilk or its effects on breastfed infants have not been well studied. Limited data indicate that

filgrastim and a similar G-CSF product, lenograstim, are poorly excreted into breastmilk and are undetectable by 3 days after an injection. Some authors recommend withholding breastfeeding for this period of time. However, filgrastim has been safely given orally to neonates and is not orally absorbed by neonates, so any filgrastim that is excreted into milk is unlikely to adversely affect the breastfed infant.

- Risk Summary for Neulasta
 - It is not known whether pegfilgrastim is secreted in human milk. Other recombinant G-CSF products are poorly secreted in breast milk, and G-CSF is not orally absorbed by neonates. Caution should be exercised when administered to a nursing woman.
- Risk Summary for Leukine
 - There is no information regarding the presence of Leukine in human milk, the effects on the breastfed child, or the effects on milk production. Administration of LEUKINE to rabbits during lactation resulted in reduction in postnatal offspring survival [see [DATA](#)]. Because of the potential for serious adverse reactions advise a lactating woman not to breastfeed during treatment and for at least 2 weeks after the last dose.
- **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 1.2017, April 28, 2017](#). 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](#))

