Myeloid Cytokines for Treatment of Acute Exposure to Myelosuppressive Doses of Radiation: Hematopoietic Subsyndrome of Acute Radiation Syndrome (H-ARS)

Key Clinical Information

- The goals of using a myeloid colony-stimulating factor for radiation-induced myelosuppression are to:
  - Improve survival of adults and children exposed to myelosuppressive doses of radiation
  - Shorten the duration of severe neutropenia
  - Minimize the severity of neutropenia-associated complications, including infection

- Initiation of treatment in a radiation incident should be strongly considered for patients who:
  - Are likely to have received ≥2 gray (Gy) whole body exposure or ≥2 Gy significant partial body exposure
  - Are likely to have an absolute neutrophil count of ≤500 cells/mm$^3$
  - Will likely have prolonged periods of significant neutropenia (See radiation effects on blood counts diagram).
  - Have significant radiation exposure plus trauma and/or burns, which worsens the clinical outcome compared to radiation exposure alone.

- The CDC is responsible for creating and issuing Emergency Use Instructions (EUIs) regarding drug use in emergencies.
  - The EUI authority allows CDC to facilitate the availability of streamlined information about the use of eligible, approved MCMs needed during public health emergencies without FDA needing to issue an Emergency Use Authorization (EUA).

<table>
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<tr>
<th>Cytokine</th>
<th>Key Information</th>
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| G-CSF: filgrastim (Neupogen drug label, Revised 06/18) | - **Estimate a patient's absorbed radiation dose** (i.e., level of radiation exposure) based on radiation dose reconstruction information, 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 ≥2 Gy. Do NOT delay administration of Neupogen if a complete blood count (CBC) is not readily available. |
### Standard dosing when supplies are adequate

- **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.**

- **Vial sizes are 300 mcg and 480 mcg. For a 70 kg person, 2 vials of either size would be the appropriate dose. It would be reasonable to indicate a maximum dose like 960 mcg OR two vials per dose though this is not uniformly agreed upon. Note that if the appropriate dose requires administration of 2 vials, separate injection sites would be required.**

- **See [FDA-approved drug label for full prescribing information](https://www.accessdata.fda.gov/drugsatfda/index.cfm?setid=4f9f0240-6550-4f6a-a8c1-d2d6426f8954).**

### Strategies for dosing when drug supplies are insufficient to treat all patients at full dose, with plan to return to standard dosing as soon as adequate drug supplies arrive

- **The standard starting dose for children is 5 mcg/kg which is then titrated for effect as needed.**

- **For adults, start with the lower dose of 5mcg/kg/day instead of 10 mcg/kg/day; dose less frequently than daily until adequate supplies arrive to treat all patients at the higher daily dose; stopping drug 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. Do NOT delay administration of Neupogen if a CBC is not readily available.

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**Pegylated G-CSF: pegfilgrastim (Neulasta drug label, Revised: 04/2019)**

- **Estimate a patient's absorbed radiation dose** (i.e., level of radiation exposure) based on **radiation dose reconstruction information, biodosimetry**, if available, or **clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.**

- **Administer Neulasta** as soon as possible after suspected or confirmed exposure to radiation doses ≥2 Gy. Do NOT delay administration of Neulasta if a CBC is not readily available.
### Standard dosing - when supplies are adequate

- 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. Administer two doses of drug subcutaneously one week apart.

- 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.

### Strategies for dosing when drug supplies are insufficient to treat all patients at full dose, with plan to return to standard dosing as soon as adequate drug supplies arrive

- Senior medical incident 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 recommend NOT administering the second dose if the ANC exceeds 5,000/mm$^3$ ($= 5.0 \times 10^9$ cells/L). These recommendations, however, are NOT included in the FDA drug label.

### Lab monitoring

- If possible, obtain a baseline CBC with differential 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/mm$^3$ ($= 5.0 \times 10^9$ cells/L), regardless of drug scarcity. Do NOT delay initial administration of Neulasta if a CBC is not readily available.

### Estimate a patient's absorbed radiation dose

(i.e., level of radiation exposure) based on radiation dose reconstruction information, 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 ≥2 Gy.

### Standard dosing

Leukine is a subcutaneous injection administered once daily as follows:

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**GM-CSF: sargramostim (Leukine drug label, Revised 03/2018)**
- 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/mm\(^3\) (\(= 1.0 \times 10^9\) cells/L) for 3 consecutive CBCs or exceeds 10,000/mm\(^3\) (\(= 10 \times 10^9\) 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/mm\(^3\) for three consecutive CBCs. Do NOT delay initial administration of Leukine if a CBC is not readily available.

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<th>G-CSF = granulocyte colony-stimulating factor</th>
<th>GM-CSF = granulocyte-macrophage colony-stimulating factor</th>
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### 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, as of February 11, 2019, for the specific indication of acute exposure to myelosuppressive doses of radiation.**
  - **tbo-filgrastim (Granix)** (Teva)
    - Granulocyte colony-stimulating factor (G-CSF)
    - Was licensed initially for clinical use in the US by the [FDA in August 2012](https://www.fda.gov/Drugs/InformationOnDrugs/ucm391655.htm).
    - Drug labeling was updated to reflect licensing for [self-administration by patients and caregivers in December 2014](https://www.fda.gov/Drugs/ApprovedDrugs/ucm391655.htm).
    - [Drug label for tbo-filgrastim](https://www.fda.gov/downloads/drugs/labelsonmedication/ucm391655.pdf) (PDF - 1.6 MB)
  - **filgrastim-sndz (Zarxio™)** (Sandoz/Novartis)
    - Granulocyte colony-stimulating factor (G-CSF)
    - FDA licensed 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](https://www.fda.gov/downloads/drugs/labelsonmedication/ucm391655.pdf) (PDF - 2.9 MB)
  - **pegfilgrastim-jmdb (Fulphila™)** (Mylan GmbH)
- FDA licensed pegfilgrastim-jmdb, as biosimilar to US-licensed Neulasta on June 4, 2018.
  - Drug label for pegfilgrastim-jmdb
- filgrastim-aafi (NIVESTYM) (Hospira/Pfizer)
  - FDA licensed filgrastim-aafi, as biosimilar to US-licensed Neupogen on July 20, 2018
  - Drug label for filgrastim-aafi

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.
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. Updates and changes to the stockpile reserves may occur from time to time.
    - 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 from the use of these drugs in other indications that support use in acute exposure to myelosuppressive doses of radiation.
  - 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.

- 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 medical incident 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 $5,000/mm^3$ ($= 5.0 \times 10^9$ cells/L) rather than $10,000/mm^3$ ($= 10.0 \times 10^9$ cells/L). These recommendations, however, are NOT included in the FDA drug label.
  - **Neulasta**: Senior medical incident 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 $5,000/mm^3$ ($= 5.0 \times 10^9$ 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.
  - Available data with Neulasta use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal studies, however, there were signs of increased embryolethality...
and spontaneous abortions occurring simultaneously with signs of maternal toxicity in pregnant rabbits.

- Available data from published studies, including several observational studies of pregnancy outcomes in women exposed to filgrastim products with Neupogen use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal studies, however, filgrastim has been shown to have adverse effects in pregnant rabbits.

- Available data with Leukine use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, however, there were signs of increased embryolethality and spontaneous abortion at doses that were not toxic to the mother in pregnant rabbits. Advise pregnant women of the potential risk to a fetus.

- Animal reproduction studies have shown an adverse effect on the fetus and/or mother 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**
    - There is published literature documenting transfer of filgrastim into human milk. There are a few case reports describing the use of filgrastim in breastfeeding mothers with no adverse effects noted in the infants. There are no data on the effects of filgrastim on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be
considered along with the mother’s clinical need for Neupogen and any potential adverse effects on the breastfed child from Neupogen or from the underlying maternal condition.

- **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. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Neulasta and any potential adverse effects on the breastfed child from Neulasta or from the underlying maternal condition.

- **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. 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**

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.)