

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

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Myeloid Cytokines

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/mm³
 - 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).

Cytokine	Key Information
<p style="text-align: center;">G-CSF: filgrastim (Neupogen drug label, Revised 06/18)</p>	<ul style="list-style-type: none"> • 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. Obtain CBC with differential prior to initiating cytokine administration when lab and drug supplies are adequate. • 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 <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. ○ 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. • 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 <ul style="list-style-type: none"> ○ 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

	<p>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.</p>
<p>Pegylated G-CSF: pegfilgrastim (Neulasta drug label, Revised: 04/2019)</p>	<ul style="list-style-type: none"> • 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. Obtain CBC with differential prior to initiating cytokine administration when lab and drug supplies are adequate. • 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 <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. 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 <ul style="list-style-type: none"> ○ 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/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 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

	<p>greater than 5,000/mm³ (= 5.0 x 10⁹ cells/L), regardless of drug scarcity. Do NOT delay initial administration of Neulasta if a CBC is not readily available.</p>
<p>GM-CSF: sargramostim (Leukine drug label, Revised 03/2018)</p>	<ul style="list-style-type: none"> • 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. Obtain CBC with differential prior to initiating cytokine administration when lab and drug supplies are adequate. • 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: <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 when Leukine supply is scarce - Obtain a baseline CBC with differential if possible, and then serial CBCs approximately every third day until the ANC remains greater than 1,000/mm³ for three consecutive CBCs. Do NOT delay initial administration of Leukine if a CBC is not readily available.

G-CSF = granulocyte colony-stimulating factor

GM-CSF = granulocyte-macrophage 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, as of June 22, 2020, 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](#).

- 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 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](#) (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](#)
- **pegfilgrastim-apgf (NYVEPRIA™)** (Hospira/Pfizer)
 - FDA licensed pegfilgrastim-apgf, as biosimilar to US-licensed Neulasta on June 10, 2020.
 - [Drug label for pegfilgrastim-apgf](#)
- **pegfilgrastim-bmez (ZIEXTENZO™)** (Sandoz/Novartis)
 - FDA licensed pegfilgrastim-bmez, as biosimilar to US-licensed Neulasta on November 4, 2019.
 - [Drug label for pegfilgrastim-bmez](#)
- **pegfilgrastim-cbqv (UDENYCA™)** (Coherus BioSciences)
 - FDA licensed pegfilgrastim-cbqv, as biosimilar to US-licensed Neulasta on November 2, 2018.
 - [Drug label for pegfilgrastim-cbqv](#)

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 of acute exposure to 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 to 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). Updates and changes to the stockpile reserves may occur from time to time.
- 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/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 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/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.
 - 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 embryoletality 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 embryoletality 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

- 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](#))

See: REMM Bibliography for Acute Radiation Injury > [Myeloid Cytokine Section](#)

Platelet Cytokine

Key Clinical Information

- **Romiplostim (NPlate®)** was approved by the FDA on January 28, 2021, as a treatment to increase survival in adult and pediatric patients (including term neonates) exposed to myelosuppressive doses of radiation, the hematopoietic subsyndrome ARS ([H-ARS](#)).
 - H-ARS is a new indication for this drug which was originally approved in 2008 for certain forms of thrombocytopenia.
 - See new [2021 FDA drug label for romiplostim](#).
- What is romiplostim?
 - Thrombopoietin Receptor Agonist (TPO-RA)
 - Member of the TPO mimetic class, romiplostim is an Fc-peptide fusion protein (peptibody)
 - Has no amino acid sequence homology to endogenous TPO
 - Produced by recombinant DNA technology in *Escherichia coli* (*E. coli*)
 - Increases platelet production through binding and activation of the TPO receptor, a mechanism analogous to endogenous TPO
 - Originally approved by the FDA in 2008 for the treatment of “thrombocytopenia in patients with chronic immune thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy”.
 - FDA also approved it in 2018 for pediatric patients one year of age and older with immune thrombocytopenic purpura (ITP) for at least 6 months who have had insufficient response to a prior therapy.
 - Additional studies suggest that romiplostim may also be effective in raising platelet counts when thrombocytopenia occurs due to a pathophysiology other than ITP.
- What is the recommended dose of romiplostim for H-ARS?
 - **Dose: 10 mcg/kg administered once as a subcutaneous injection.**
 - Administer the dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation
 - The FDA drug label says that for treatment of myelosuppressive doses of radiation:

- “Administer romiplostim regardless of whether a complete blood count (CBC) can be obtained.”
 - “Estimate a patient’s absorbed whole body 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.”
- The 10 mcg/kg dosing regimen for humans is based on population modeling and simulation analyses.
 - Because of the uncertainty associated with extrapolating animal efficacy data to humans, the selection of a human dose for romiplostim is aimed at providing platelet response to romiplostim that is similar to that observed in efficacy studies conducted in animals.
 - **For pediatric patients** (including term neonates), extrapolation was based on data supporting romiplostim’s effect on thrombocytopenia in patients with ITP and an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
 - A similar response to romiplostim is expected in the pediatric and adult patients based on the mechanism of action of the drug and pharmacokinetics of romiplostim in pediatric patients 1 year and older with ITP
- More about using romiplostim for H-ARS
 - The FDA approval of romiplostim for H-ARS was based on efficacy studies conducted in adult animals, accordance with the [animal rule](#), as noted in the study below by Wong et al.
 - Efficacy studies of romiplostim could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons.
 - For this reason, the pharmacokinetics of romiplostim is not available in patients acutely exposed to myelosuppressive doses of radiation.
 - According to the FDA drug label...
 - “The *safety* of romiplostim for the acute radiation syndrome setting was based on the clinical experience in patients with ITP and from a study with healthy volunteers.”
 - “The *efficacy* of romiplostim was studied in a randomized, blinded, placebo-controlled study in a non-human primate model of radiation injury.”
 - The primary efficacy endpoint was survival.

- Romiplostim significantly (one-sided $p = 0.0002$) increased 60-day survival in the irradiated animals: **72.5%** survival (29/40) in the romiplostim group compared to **32.5%** survival (13/40) in the control group.
- In the same study, an exploratory cohort of $n=40$ animals received romiplostim (5mg/kg) on day 1 **and** pegfilgrastim (0.3mg/kg) on days 1 and 8 post-irradiation. Survival in this combined treatment group was **87.5%** (95% CI: (73.2%, 95.8%)).
- See the [drug label](#) for patient counseling information, contraindications, side effects/adverse effects/toxicities, drug interactions, use and concerns in specific populations including pregnant and lactating women and details about preparation and administration.
- **See:** REMM Bibliography for Acute Radiation Injury > [Platelet Cytokine Section](#)

