Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Granulocyte or Granulocyte-Macrophage Colony Stimulating Factors

Filgrastim (Neupogen)
Filgrastim-aafi (Nivestym)
Filgrastim-ayow (Releuko)
Filgrastim-sndz (Zarxio)
Tbo-filgrastim (Granix)
Pegfilgrastim (Neulasta)
Pegfilgrastim-jmdb (Fulphila)
Pegfilgrastim-apgf (Nyvepria)
Pegfilgrastim-cbqv (Udenyca)
Pegfilgrastim-bmex (Ziextenzo)
Sargramostim (Leukine)

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Executive Summary

Recombinant human granulocyte colony-stimulating factors (G-CSFs) and granulocyte-macrophage colony-stimulating factor (GM-CSF), collectively called CSFs, are hematopoietic growth factors that stimulate the production and differentiation of progenitor cells, along with enhancing the function of some end-target cells.[1] Short-acting G-CSFs include filgrastim (Neupogen), its U.S. Food and Drug Administration (FDA)-approved biosimilars (filgrastim-aafi [Nivestym], filgrastim-ayow [Releuko], and filgrastim-sndz [Zarxio]), and tbo-filgrastim (Granix), which is similar to filgrastim, but is not an FDA-approved biosimilar. Long-acting G-CSFs include pegfilgrastim (Neulasta) and its FDA-approved biosimilars, pegfilgrastim-jmdb (Fulphila), pegfilgrastim-apgf (Nyvepria), pegfilgrastim-cbqv (Udenyca), and pegfilgrastim-bmez (Ziextenzo). Pegfilgrastim is formed by the addition of a polyethylene glycol molecule to filgrastim which extends the duration of action, particularly during neutropenia, since elimination of the pegylated form is primarily dependent on circulating neutrophils.[2] Sargramostim (Leukine) is a GM-CSF. Unlike G-CSFs that primarily affect development and function of neutrophils,[3] GM-CSF *additionally* affects development of macrophages and myeloid-derived dendritic cells, and enhances of the function of these cells along with eosinophils.[4]

The FDA-approved biosimilars have demonstrated sufficient evidence to be considered lacking meaningful differences in safety or efficacy compared to the reference product (filgrastim or pegfilgrastim) by the FDA.[5] The G-CSF biosimilars possess the same FDA-approved indications as the originator product except for any indications where the reference product maintains exclusive rights.

An FDA-approved use for G-CSFs is to decrease the incidence of infection/febrile neutropenia (FN) and/or to reduce the duration of neutropenia in patients with non-myeloid malignancies (eg, solid tumors, lymphoma, non-myelogenous leukemias) receiving myelosuppressive chemotherapy. Chemotherapy-induced neutropenia (CIN), usually measured by the absolute neutrophil count (ANC), increases morbidity and mortality. It can have deleterious effects both due to infections, and from a negative impact on delivery of an optimal dose of chemotherapy at the planned frequency.[6] Mortality risk with FN varies based on type of infection, comorbidities, type of cancer, and age; the rate may be as high as 50% in patients with multiple major comorbidities.[7] CSFs may also be used to mobilize hematopoietic progenitor cells in the peripheral blood for a peripheral blood stem cell transplant (PBSCT). PBSCT or bone marrow transplant (BMT), both types of hematopoietic cell transplants (HCT), are potentially life-saving procedures for malignancies (primarily hematologic cancers) and non-malignant conditions (eg, bone marrow-related or immune system-related disorders).[8] For an *autologous* transplant, the donor and recipient are the same person, whereas for an *allogeneic* transplant, transplanted cells are from someone else, generally, a healthy, matched donor.[9]

FDA-approved indications for the CSFs are as follows **(* indicates a use for the original product only):**

- **Filgrastim and filgrastim biosimilars**[3,10-12]: (1) to decrease the risk of FN in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy with a high incidence of neutropenia; (2) to decrease the time to neutrophil recovery and length of fever in acute myeloid leukemia (AML) patients receiving chemotherapy; (3) mobilization of progenitor stem cells for collection by apheresis in the setting of autologous stem cell transplants[†]; (4) to reduce

[†] Two filgrastim biosimilars (filgrastim-aafi and filgrastim-sndz) share this FDA-indication with filgrastim, but the newest filgrastim biosimilar, filgrastim-ayow, does not.

the duration of neutropenia/related sequalae in patients with a non-myeloid malignancy who receive myeloablative chemotherapy followed by a bone marrow transplant (BMT); (5) treatment of hematopoietic syndrome of acute radiation (H-ARS) for increased survival*; (6) to decrease neutropenic complications in patients with rare disorders characterized by symptomatic severe chronic neutropenia (SCN)

- **Tbo-filgrastim**[13]: (1) to reduce severe neutropenia duration in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy with a high incidence of neutropenia (age ≥ 1 month)
- **Pegfilgrastim and pegfilgrastim biosimilars**[14-18]: (1) to decrease the risk of FN in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy with a high incidence of neutropenia; (2) treatment of H-ARS for increased survival*
- **Sargramostim**[4]: (1) to shorten time to neutrophil recovery and reduce incidence of infectious complications after *induction* chemotherapy for AML (age ≥ 55 years); (2) mobilization of progenitor stem cells for collection by apheresis in the setting of autologous stem cell transplants (adults); (3) treatment of H-ARS for increased survival; for faster myeloid reconstitution after: (4) autologous PBSCT or BMT in patients with non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, or acute lymphoblastic leukemia (ALL) [age ≥ 2 years] or (5) after allogeneic BMT from a matched related donor (age ≥ 2 years); (6) for *treatment* of delayed/failed neutrophil grafts after allogeneic or autologous BMT

Filgrastim and sargramostim have the most FDA-approved indications, at 6 each. Most of these products are indicated for all ages. Exceptions include tbo-filgrastim (for age ≥ 1 month), and sargramostim, for which the age for use varies by indication, as shown above. Prophylaxis of FN (eg, decreasing the risk of its occurrence, or limiting the duration of severe neutropenia) in patients with a non-myeloid malignancy after myelosuppressive chemotherapy is a common indication shared by all G-CSFs, but not sargramostim. Pegfilgrastim, filgrastim, and sargramostim are all indicated for treatment of H-ARS. Filgrastim and sargramostim share similar indications (exact wording may differ) for mobilization of progenitor stem cells, neutrophil recovery after chemotherapy in AML patients, and for reducing neutropenic sequelae after an autologous BMT (sargramostim and filgrastim) or PBSCT (sargramostim). Unlike other CSFs, filgrastim and its biosimilars are approved for the chronic treatment of severe chronic neutropenia disorders such as congenital neutropenia or idiopathic neutropenia, which are rare disorders for which G-CSF is considered a first-line therapy.[19] Sargramostim is uniquely FDA-indicated for myeloid reconstitution support after an allogeneic BMT, and for the treatment of delayed or failed neutrophil recovery after an autologous or allogeneic BMT.

The recommended dose and route of administration (for filgrastim, filgrastim biosimilars and sargramostim) varies by indication. In general, filgrastim, filgrastim biosimilars, tbo-filgrastim, and sargramostim require dosing at least once daily. These products are also given as a weight-based or body-surface area based (sargramostim) dose. In contrast, pegfilgrastim and pegfilgrastim biosimilars are given as a fixed-dose of 6 mg for people weighing >45 kg and are given less frequently (eg, once per chemotherapy cycle). Filgrastim, filgrastim biosimilars, and sargramostim can be given subcutaneously (subQ) or intravenously (IV), depending on indication. When possible, for G-CSFs, the subQ route is generally preferred.[20,21] Pegfilgrastim, pegfilgrastim biosimilars, and tbo-filgrastim are for subQ use only. All products can be self- or caregiver-administered subQ with appropriate training. In children weighing

<45 kg, weight-based doses of pegfilgrastim are recommended. The manufacturer's recommend avoiding *direct* administration of these products to people weighing <45 kg using the standard pre-filled syringe (containing 6 mg) because the syringe is not graduated and dosing errors may occur.

Most of the CSFs are available as single-dose prefilled syringes with or without additional availability as vials except for sargramostim which is only available as vials. A unique formulation for pegfilgrastim (and not pegfilgrastim biosimilars) is the on-body injector (OBI) [Neulasta Onpro kit]. This OBI can be secured to a patient's skin by a healthcare provider and will subcutaneously deliver pegfilgrastim approximately 27 hours after placement.

Guideline Recommendations and Potential Off-Label Uses per Micromedex

Reviewed US guidelines from the National Comprehensive Cancer Network (NCCN) [2021 or 2022‡] address most on-label uses of CSFs and provide recommendations for off-label uses in oncology patients (we will focus on mentioning off-label uses that are part of the NCCN Drug and Biologics Compendium§,[22]; consult the guideline summary [page 25] and off-label use section [page 46] for additional details). Guidelines from the American Society for Transplantation and Cellular Therapy (ASTCT) [2014], and American Society of Clinical Oncology (ASCO) [2015, 2021] were also reviewed.

Both the NCCN (2021) and the ASCO (2015) recommend a CSF (NCCN specifies G-CSF) for FN *primary prophylaxis* for adults with solid tumors or lymphoma receiving *high-risk* (ie, estimated incidence of FN ~20% or higher) chemotherapy.[20,21] Primary prophylaxis for these patients is also recommended by the NCCN for *intermediate-risk* (10-20% FN incidence) chemotherapy regimens in patients with ≥ 1 patient risk factor (eg, older age, organ dysfunction, recent surgery, prior chemotherapy/radiation)[20]; and by ASCO, when FN risk is expected to be ≥ 20% based on a combination of chemotherapy and patient or disease factors. CSF primary prophylaxis is also recommended by ASCO when it may enable delivery of dose-dense chemotherapy, when there is evidence of a survival benefit in well-designed trials, or for older adults (≥ 65 years) receiving potentially curative chemotherapy for diffuse aggressive lymphoma.[21] *Secondary prophylaxis* (ie, during the 2nd or later chemotherapy cycle), is generally recommended by ASCO and NCCN for patients that experienced neutropenia-related complications in a prior chemotherapy cycle (in the absence of CSF prophylaxis), if use of the CSF could affect their disease outcome.[20,21] The ASCO states that the approach for adults can generally be extended to children, or otherwise, CSF should be used in children according to clinical protocols.[21] The NCCN recommends FN prophylaxis with pegfilgrastim, filgrastim, or their biosimilar for certain chemotherapy regimens for Wilm's tumor (common in children).[23] For FN prophylaxis after myelosuppressive chemotherapy, primarily aimed at adults with solid tumors/lymphoma, both the NCCN and ASCO consider all G-CSFs to be effective options.[20,21] The ASCO notes that "…choice of agent depends on convenience, cost, and clinical situation."[21]

CSFs may also be considered as supportive care for drug-associated toxicities,[24-29] for mobilization of peripheral blood stem cells,[21,30,31] or as supportive care (G-CSFs) after an autologous (or allogeneic for CSFs in general per ASCO[21]) transplant (see guideline section starting on page 25 for details about these

‡ NCCN guidelines are frequently updated (minimum of once per year). Accessed guidelines were current as of the date listed among our references (mostly January 2022). Consult the NCCN website for current guidelines.
§ This resource compiles NCCN guideline recommendations by product when guidelines recommend a specific CSF (instead of more generally, 'growth factors', for example). The compendium is a recognized authority for drug policy by some payors, including the Center for Medicare and Medicaid Services.

uses).[32] All CSFs are an option for treatment of hematopoietic acute radiation syndrome.[20,21,33] In general, guidelines recommend CSFs as adjunctive treatment of infections and/or FN in patients that are not responding to standard therapy, or who are high-risk for poor outcomes.[20,34-37] CSFs are not routinely recommended for adult cancer patients with afebrile neutropenia.[20,21]

Filgrastim is listed as an option by the NCCN for nearly all recommended uses for CSFs; one exception is for use with a chemotherapy regimen for a type of lymphoma, when sargramostim is an option.[25] Below is a summary of NCCN guideline-listed uses for CSFs contrasted with filgrastim:

- Sargramostim is recommended for the fewest oncology-related indications. Most recommendations for sargramostim are in the setting of adjunctive treatment for FN/infections, or for mobilization of stem cells for autologous HCT in combination with other agents. The only reviewed NCCN-listed indication where sargramostim and not another CSF is recommended, is for combined treatment with a particular chemotherapy regimen for Richter's transformation, a type of diffuse large B-cell lymphoma.[25]
- Pegfilgrastim is recommended by NCCN for fewer indications than filgrastim. A recommended off-label use for pegfilgrastim by the NCCN is co-mobilization of stem cells with plerixafor for autologous donors, a potential use shared with filgrastim or its biosimilars and tbo-filgrastim.[30]

  Below are some indications where filgrastim is listed as an option by NCCN, and pegfilgrastim is <u>not</u>:

  - Treatment of FN (per NCCN guideline primarily aimed at adults with solid tumors/lymphoma, pegfilgrastim has only been studied for prophylaxis)[20]
  - FN prophylaxis (in guideline aimed at adults with solid tumors/lymphoma) for chemotherapy regimens requiring *weekly cycles* (per NCCN, lack of evidence with pegfilgrastim)[20]
  - Induction chemotherapy for adults with AML[24]
  - Mobilization of stem cells as *monotherapy* in adult (or pediatric according to the ASTCT, 2014[31]) *autologous* or *allogeneic* donors[30]
  - Treatment of symptomatic anemia in adults with low-risk myelodysplastic syndromes[36]
  - Supportive care for CAR-T therapy associated neutropenia[27]
- Regarding biosimilars and tbo-filgrastim, various NCCN guidelines take different approaches about whether they extend any recommendations for the originator product to similar products. The NCCN recognizes filgrastim biosimilars as a substitution for filgrastim for most indications. Tbo-filgrastim is recognized as a substitution for filgrastim by NCCN for many uses, but for fewer indications than the filgrastim biosimilars (for example, <u>not</u> for AML induction chemotherapy[24] or CAR-T therapy associated neutropenia[27]). Pegfilgrastim biosimilars are an option for recommended uses for pegfilgrastim by the NCCN.

Micromedex includes a list of recommended, off-label uses for filgrastim, pegfilgrastim, and sargramostim. A level IIa recommendation (intended to be appropriate for most cases) is assigned to 2 indications: filgrastim for patients with leukemia, especially "…as an alternative or adjunct to donor leukocyte infusions in patients with leukemic relapses after allogeneic stem-cell transplantation"[38] and

for pegfilgrastim, mobilization of peripheral blood stem cells before *autologous* HCT. More level IIb recommendations (intended to be appropriate in *some* cases) are assigned for filgrastim off-label uses (12) than for sargramostim (9) or pegfilgrastim (0) off-label uses.[38-40] Table 11 (page 46) of the report summarizes the Micromedex recommended off-label uses.

Safety and Warnings/Precautions

The safety profile among G-CSFs is expected to be similar even if some events have occurred with one product and not another.[20] The most common drug-related adverse event (AE) is mild to moderate short-term bone or musculoskeletal pain. Relative tolerability of sargramostim to G-CSFs is not well-established since there are few direct comparative randomized studies. Myalgia, arthralgia, or bone pain has also been reported with sargramostim.[4] Filgrastim is partially dependent on renal excretion and may accumulate in patients with end-stage renal disease. Concerning use during pregnancy, the most in-human observational data is with filgrastim, and suggests that it is compatible with pregnancy and probably compatible with breast-feeding.[41]

All products are contraindicated in patients with allergies to the product or similar products (for sargramostim, this includes yeast allergies). The syringe of some G-CSF products (filgrastim, filgrastim-sndz, pegfilgrastim, pegfilgrastim-bmez) is made with natural rubber and should be avoided in patients with latex allergies. Sargramostim formulations containing benzyl alcohol (multi-dose vial) should be avoided during pregnancy or for infants.

All CSFs carry similar labeled warnings/precautions for the possibility of serious allergic reaction, development of leukocytosis which necessitates laboratory monitoring, development of capillary leak syndrome (and effusions for sargramostim), and the potential to stimulate growth of malignant cells (especially for myeloid malignancies). For filgrastim/biosimilars, tbo-filgrastim, and sargramostim, there is a labeled warning to avoid administration within 24 hours of chemotherapy (or radiation for sagramostim); for the others, there is a lack of evidence for concurrent use with radiotherapy. Pegfilgrastim/biosimilars do not carry a warning for time of administration, but are not recommended for administration 14 days before or within 24 hours after chemotherapy. **Other warnings unique to sargramostim** include the risk for infusion-related reactions, reported cases of neutralizing anti-drug antibodies (use of the shortest needed duration is recommended), and supraventricular arrythmias. **Warnings unique to all G-CSF products include** the potential for fatal splenic rupture; cases of acute respiratory distress syndrome; severe sickle cell crises in patients with sickle cell disorders; glomerular nephritis; aortitis; and transient changes in bone-imaging. **Warnings unique to various G-CSF products include** alveolar hemorrhage/hemoptysis in healthy peripheral blood progenitor cell donors (filgrastim or biosimilar, tbo-filgrastim); development of secondary malignancies including myelodysplastic syndromes and AML among breast/lung cancer patients ([peg]filgrastim or biosimilars) or severe chronic neutropenia patients (filgrastim or biosimilar); and thrombocytopenia requiring monitoring of platelets ([peg]filgrastim or biosimilars). **A unique warning for filgrastim/biosimilars** is the risk for cutaneous vasculitis, especially among patients with severe chronic neutropenia receiving chronic treatment. **Unique warnings for the pegfilgrastim OBI device** include the risk for allergic reactions in patients with an acrylic adhesive allergy and the potential for device failure resulting in a missed or partial pegfilgrastim dose.

Direct Comparative Evidence

Randomized controlled trials (RCTs) comparing CSFs to one another, or systematic review meta-analyses (SRMAs) of such RCTs with direct comparisons were reviewed. The identified SRMAs, particularly those conducted among patients receiving a G-CSF for prophylaxis of CIN/FN during myelosuppressive chemotherapy, included heterogeneous RCTs with respect to the exact product (eg, including similar "long-acting" G-CSFs together in the pegfilgrastim arm), time of G-CSF initiation and duration of treatment (for filgrastim), and G-CSF doses, with few RCTs comparing G-CSF regimens consistent with US prescribing information. Owing to this heterogeneity, we cannot be sure that the results from these SRMAs are generalizable to US practice and available products.

There is a paucity of comparative evidence among children and adolescents. One RCT compared filgrastim to pegfilgrastim for CIN/FN prophylaxis in children or young adults with sarcomas,[42] and the other compared these treatments for neutrophil recovery support after an autologous peripheral blood stem cell transplant[43]; both demonstrating similar efficacy and safety between the studied G-CSFs.

Filgrastim (or similar short-acting G-CSF) vs pegfilgrastim (or similar long-acting G-CSF)[**]:

Prophylaxis of CIN/FN in patients with primarily non-myeloid malignancies: Five SRMAs that include between 7-16 RCTs each compared subQ pegfilgrastim (or a similar long-acting G-CSF) at various doses to subQ filgrastim (or a similar short-acting G-CSF) at various doses, primarily among adults with solid tumors or lymphoma.[44-48] Overall, these studies suggest that a once-per-chemotherapy cycle dose of pegfilgrastim is at least as effective and possibility superior to daily doses of filgrastim (given for variable durations, most often a minimum of 7 doses[47] if not 10-11 doses[49,50]) for reducing the incidence of febrile neutropenia.[44-48] The 5 SRMAs were inconsistent regarding the statistical superiority of pegfilgrastim over filgrastim for FN prevention, although the direction of the pooled effect was consistent, tending to favor pegfilgrastim.[44-48] Two RCTs (one among adults with breast cancer[51] and the other among children and young adults with sarcomas[42]) which used US products at approximately the recommended dosing regimen also reported a numeric benefit favoring pegfilgrastim, but failed to establish a significant difference; they may have been underpowered to detect any difference for this outcome. The larger RCT in adults established the noninferiority of pegfilgrastim (6 mg/cycle subQ) to filgrastim (5 mcg/kg subQ until ANC recovery) for the mean duration of severe neutropenia.[51] A statistically significant benefit favoring either treatment was not observed for any other efficacy outcome reported by SRMAs, including incidence of severe (eg, grade 3 or grade 4) neutropenia[44-46] and time to ANC recovery.[45,46] SRMAs comparing pegfilgrastim and filgrastim suggest that these G-CSFs carry similar risks of common AEs (ie, bone pain, or myalgia).[44-46] One RCT of the US-recommended doses of pegfilgrastim and filgrastim in adults with breast cancer reported a numerically higher rate of severe bone pain in the filgrastim versus pegfilgrastim arm.[51]

Refer to the direct comparative evidence section (page 54) of the report for studies that either failed to demonstrate significant differences or reported noninferiority in the following populations for daily filgrastim vs single-dose pegfilgrastim:

[**] Some SRMAs and/or RCTs may have included 'similar' (eg, a US-biosimilar, non-US biosimilar or non-biosimilar product with similar properties) G-CSF products to the originator filgrastim or pegfilgrastim. While studies tended to describe filgrastim as filgrastim, we could not verify the product's origin for all studies owing to lack of reporting by study authors. In a few cases, studies reported using a long-acting G-CSF which was not US pegfilgrastim.

- **Prophylaxis of CIN/FN among AML patients** (1 phase 2 RCT[52]; page 56)
- **Mobilization of peripheral blood stem cells (mostly in combination with chemotherapy) for autologous HCT** (1 SR of 6 RCTs[53] and 1 other RCT[54], primarily of very low or low quality; page 57)
- **Neutrophil recovery support after autologous PBSCT** (2 SRs[55,56] with total of 6 RCTs; page 57)

Filgrastim or pegfilgrastim vs their biosimilar; or filgrastim vs tbo-filgrastim (all G-CSFs):

SRMAs of head-to-head studies of filgrastim[44,57,58] or pegfilgrastim[57-59] compared to their respective biosimilars (or similar product[††]) suggest comparable efficacy and safety profiles related to primary prevention of FN in patients receiving chemotherapy, mostly adults with breast cancer or lymphoma. One RCT compared filgrastim to filgrastim-sndz, both given IV, for mobilization of PBSCs in adults with hematologic malignancies undergoing autologous PBSCT, demonstrating comparable efficacy and safety.[60]

In addition, a MA of 3 RCTs demonstrated similar efficacy of tbo-filgrastim to the originator filgrastim for primary prevention of FN in patients receiving chemotherapy[61]; a phase 2 RCT also suggested similar efficacy, when combined with the co-mobilizer plerixafor, to mobilize CD34+ cells for autologous HCT.[62] Overall, the safety profile between filgrastim and tbo-filgrastim was similar for prevention of FN among solid tumor or lymphoma patients,[63-65] and in multiple myeloma or lymphoma patients receiving CSF for mobilization of stem cells for autologous transplant.[62] In a trial among breast cancer patients, the overall AE incidence was significantly higher with filgrastim than tbo-filgrastim (39.7% vs 25.7%).[63]

Filgrastim (G-CSF) vs sargramostim (GM-CSF):

No head-to-head studies were found for filgrastim vs sargramostim that compared these products at FDA-approved dosages for approved or guideline-recommended uses for at least 1 product in the comparison. Refer to the body of the report (page 59) for a description of 3 RCTs[66-68] that compared these products either with non-approved dosages or for non-routine uses.

Summary and Recommendations

US guidelines, which are primarily directed at adults with solid tumors or lymphoma, consider all G-CSFs to be an option for FN prophylaxis in patients receiving high FN-risk chemotherapy, or that are at high-risk for FN based on a combination of chemotherapy, patient, and disease factors. Selection among the G-CSFs is based on clinical or convenience factors. Robust direct comparative evidence from SRMAs of RCTs, mostly among adults with solid tumors or lymphoma, suggests that a once-per-chemotherapy cycle subQ dose of pegfilgrastim is at least as efficacious, and possibly superior for preventing febrile neutropenia, compared to daily subQ doses of filgrastim. Both products exhibit a similar safety profile. Long-acting G-CSFs like pegfilgrastim offer the convenience of less frequent dosing. Delphi-consensus formed expert recommendations (2017) favor use of pegfilgrastim for chemotherapy-induced FN prophylaxis in situations where there is a risk that filgrastim will not be continued for the duration

[††]SRMAs report use of some G-CSF products which are not a US-available biosimilar, and additionally in some cases, included tbo-filgrastim studies among pooled meta-analyses of filgrastim biosimilars.
Among the included SRs and SRMAs, there was no evidence for filgrastim-ayow (Releuko), pegfilgrastim-gbqv (Udenyca), or pegfilgrastim-apgf (Nyvepria).

studied in comparative trials (mean of 11 days, or until ANC recovery after chemotherapy), or based on patient convenience.[69]

Filgrastim and filgrastim biosimilars have more FDA-approved indications compared to pegfilgrastim or pegfilgrastim biosimilars. And although the NCCN lists pegfilgrastim as an option for some off-label uses that overlap with filgrastim indications (eg, mobilization of peripheral blood progenitor cells in autologous donors), filgrastim is considered an option by the NCCN in more circumstances.

Tbo-filgrastim is not an FDA-approved biosimilar to filgrastim, although it is a biosimilar in other countries,[70,71] and it is expected to be similar to filgrastim based on available pharmacokinetic[72] and clinical evidence.[61] RCT evidence demonstrated comparable safety and efficacy of tbo-filgrastim to filgrastim for chemotherapy-induced neutropenia prophylaxis[61] and for mobilization of PBSC for autologous HCT in combination with plerixafor, in a smaller phase 2 trial.[62] The NCCN often extends recommendations for filgrastim to tbo-filgrastim, but there are some cases where an NCCN guideline has not.

Sargramostim is the only GM-CSF, possessing different pharmacology. Like filgrastim, at least daily use is required. It is recommended by the NCCN in fewer circumstances than the G-CSFs. It possesses unique warnings relative to G-CSFs (and *vice versa),* but the comparative safety profile is not well-established.

The Utah Medicaid P&T Committee may consider the following:

1. Recommend that at least 1 short-acting G-CSF (filgrastim or an FDA-approved filgrastim biosimilar, tbo-filgrastim) and 1 long-acting G-CSF (pegfilgrastim or an FDA-approved pegfilgrastim biosimilar) be preferred on the Utah Medicaid Preferred Drug List (PDL).
    a. If the resultant PDL-preferred CSF is not FDA-approved or not recommended by a US guideline for the patient's indication, access to a non-preferred CSF that is approved for their indication should be considered through a prior authorization request.
    b. If a long-acting G-CSF is not preferred on the PDL, consider allowing access (via prior authorization) for compelling patient-specific situations in which daily administration of a short-acting G-CSF (if PDL-preferred) is not feasible or appropriate, and there is RCT evidence of sufficient quality and/or guideline recommendations supporting the long-acting G-CSF as an option for that indication.

Introduction

Recombinant human granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been used therapeutically since the 1990s.[73] The first G-CSF approved by the U.S. Food and Drug Administration (FDA) was filgrastim (Neupogen) in 1991.[3] Sargramostim (Leukine) is a GM-CSF, approved in 1991.[4] The longer-acting, pegylated form of filgrastim, pegfilgrastim (Neulasta), was approved in 2002.[14] More recently, biosimilars to the originator G-CSFs (filgrastim and pegfilgrastim) became available. This includes 3 filgrastim biosimilars, filgrastim-aafi (Nivestym), filgrastim-ayow (Releuko) and filgrastim-sndz (Zarxio),[3,10,12] and 4 pegfilgrastim biosimilars, pegfilgrastim-jmdb (Fulphila), pegfilgrastim-apgf (Nyvepria), pegfilgrastim-cbqv (Udenyca), and pegfilgrastim-bmez (Ziextenzo).[15-18] An additional G-CSF, tbo-filgrastim (Granix), is similar to filgrastim, but is not an FDA-approved biosimilar.[13,74] Under different product names, the Teva Pharmaceuticals tbo-filgrastim is approved as a biosimilar to filgrastim in Europe.[70,71,75,76] In this report, we use colony-stimulating factor (CSF) to refer collectively to all recombinant G-CSF and GM-CSF products; this review will not include the virotherapies talimogene laherparepvec and Sipuleucel-T.

Biosimilar products follow regulatory guidance for approval relative to the reference originator product. Therapeutic protein biosimilars possess the same amino acid sequence as the originator, but are allowed to slightly differ (eg, differences in glycosylation, post-translational changes to proteins, variable excipients in the formulation)[77] as long as they demonstrate that they have "…no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from an existing FDA-approved reference product."[5] FDA-approval of a biosimilar generally requires pharmacokinetic, pharmacodynamic, and immunogenicity studies.[5] In some settings, biosimilars may offer the advantage of lower cost than the reference product.[77]

None of the biosimilars in this report are approved as interchangeable (ie, allowing substitution in pharmacies without prescriber approval as permitted by state law) by the FDA[78]; interchangeability requires additional evidence beyond what is necessary to demonstrate biosimilarity.[79] Proven indications for the originator product are *generally* extended to biosimilar products unless the originator still has marketing exclusivity for a particular indication.[80] One exception to this is the newest filgrastim biosimilar, filgrastim-ayow, which is not yet approved for mobilization of autologous progenitor cells, unlike filgrastim-sndz and filgrastim-aafi.[10,12,15] Tbo-filgrastim was approved as a new biologic owing to its US approval prior to the biosimilar pathway,[74] and thus, the FDA-approved indications for tbo-filgrastim differ from filgrastim and its approved biosimilars.[3,10,11,13]

Like endogenous G-CSF and GM-CSF, recombinant CSFs stimulate the production and differentiation of target progenitor cells in the bone marrow, and they enhance the function of lineage-specific developed cells.[1,3,4,14] G-CSFs more selectively target neutrophils whereas sargramostim additionally affects eosinophils, macrophages and myeloid-derived dendritic cells.[1] These properties give CSFs many potential preventative or therapeutic applications. Filgrastim, pegfilgrastim, and sargramostim are each considered important medications for stabilization and/or curing disease; they are included in the FDA's 2020 list of essential medicines and medical countermeasures.[81]

Table 1 provides an overview of the FDA-approved indications of CSFs (see **Appendix A** for the "full" indication). Filgrastim and sargramostim are approved for the largest number of indications, 6 each.[3,4] Biosimilars to filgrastim and pegfilgrastim share the same indications as the originator product *except*

for treatment of hematopoietic syndrome of acute radiation (H-ARS)[‡‡],[10,11,15-18,82,83] which is an approved use for the originators only.[3,4,14] All G-CSFs are indicated to either reduce the risk of febrile neutropenia or to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy with a high incidence of neutropenia.[3,10,11,13-18] This is the *only* FDA-approved indication for tbo-filgrastim (for age ≥ 1 month) and pegfilgrastim biosimilars.[13,15-18] Filgrastim and filgrastim biosimilars are additionally indicated to decrease the time to neutrophil recovery and length of fever in acute myeloid leukemia (AML) patients receiving chemotherapy[3,10,11]; sargramostim shares a similar indication, but is more restrictive to only induction chemotherapy for AML patients 55 years or older.[4] Both filgrastim/filgrastim biosimilars and sargramostim (for adults only) are also indicated for mobilization of progenitor stem cells for collection by apheresis in the setting of autologous stem cell transplants.[3,10,11] A unique indication for filgrastim and its approved biosimilars is as chronic treatment to decrease neutropenic complications in patients with rare disorders characterized by symptomatic chronic neutropenia.[3,4,10,11]

Both filgrastim/filgrastim biosimilars and sargramostim have FDA-approved indications related to neutrophil recovery in patients who received a bone marrow transplant (BMT); in both cases, these CSFs are given shortly after the transplant to prevent the development of neutropenia-related complications.[3,4,10,11] Filgrastim and its biosimilars are indicated to reduce the duration of neutropenia/related sequalae in patients of any age with a non-myeloid malignancy who receive myeloablative chemotherapy followed by a BMT. Whereas, sargramostim is indicated to accelerate myeloid reconstitution (eg, recovery of neutrophils) in patients 2 years of age or older with either: certain types of lymphoma or lymphocytic leukemia who received an autologous peripheral blood progenitor cell (PBSC) or bone marrow transplant, or who received an allogeneic BMT from an HLA-matched matched donor related to the recipient.[4] Sargramostim is also uniquely indicated to *treat* patients ages 2 or older with a delayed/failed neutrophil recovery after autologous or allogeneic BMT.[4] Many additional potential off-label uses of CSFs have been identified, which are discussed in the off-label overview and clinical practice guideline sections of this report.

Alternative non-G-CSF agents with a similar indication to G-CSFs are either under development (plinabulin)[84] or FDA-approved (trilaciclib [Cosela]) as of 2021,[85] for reducing the incidence of neutropenia following myelosuppressive chemotherapy. Intravenous trilaciclib is listed by the National Comprehensive Cancer Institute (NCCN) as an option for prophylaxis of CIN for the narrow population of patients with extensive-stage small cell lung cancer in patients receiving certain chemotherapy regimens.[20] Unlike G-CSFs, it is given before receipt of chemotherapy; and it could be combined with G-CSFs (given after chemotherapy) according to the NCCN.[20]

[‡‡] Neupogen (filgrastim) and Neulasta (pegfilgrastim) retain marketing exclusivity for this indication. However, this is expected to change in 2022 (on March 30, 2022 for filgrastim and unknown date for pegfilgrastim)

Table 1. Overview of FDA-Approved Colony-Stimulating Factor Indications

Generic Name Brand	To reduce the incidence of and/or duration of neutropenic sequelae among patients with:				To mobilize hematopoietic progenitor cells for:	To increase survival in:	To accelerate myeloid reconstitution in:		To treat delayed neutrophil recovery or graft failure:
	Non-myeloid[a] malignancy on myelosuppressive chemotherapy	AML on induction or consolidation chemo	Non-myeloid[a] malignancy undergoing chemo followed by BMT	Severe chronic neutropenia	leukapheresis in *autologous* PBPC collection and therapy	Hematopoietic syndrome of acute radiation	Post auto-PBPC or BMT for NHL, ALL and HL	Allo-geneic BMT	Occurring after allogenic or autologous BMT
Short-acting granulocyte colony-stimulating factors (G-CSF)									
Filgrastim[3] **Neupogen**	X	X	X	X	X	X			
Tbo-filgrastim[13] **Granix**	X Adults Children ≥ 1 mo								
Filgrastim-aafi[10] **Nivestym**	X	X	X	X	X				
Filgrastim-ayow[12] **Releuko**	X	X	X	X					
Filgrastim-sndz[11] **Zarxio**	X	X	X	X	X				
Long-acting granulocyte colony-stimulating factors (G-CSF)									
Pegfilgrastim[14] **Neulasta**	X					X			
Pegfilgrastim-jmdb[15]	X								

Table 1. Overview of FDA-Approved Colony-Stimulating Factor Indications

Generic Name Brand	To reduce the incidence of and/or duration of neutropenic sequelae among patients with:				To mobilize hematopoietic progenitor cells for:	To increase survival in:	To accelerate myeloid reconstitution in:		To treat delayed neutrophil recovery or graft failure:
	Non-myeloid[a] malignancy on myelosuppressive chemotherapy	AML on induction or consolidation chemo	Non-myeloid[a] malignancy undergoing chemo followed by BMT	Severe chronic neutropenia	leukapheresis in *autologous* PBPC collection and therapy	Hematopoietic syndrome of acute radiation	Post auto-PBPC or BMT for NHL, ALL and HL	Allo-geneic BMT	Occurring after allogenic or autologous BMT
Fulphila									
Pegfilgrastim-apgf[18] **Nyvepria**	X								
Pegfilgrastim-cbqv[16] **Udenyca**	X								
Pegfilgrastim-bmez[17] **Ziextenzo**	X								
Granulocyte-macrophage colony-stimulating factor (GM-CSF)									
Sargramostim[4] **Leukine**		X Adults ≥ 55 (post-induction chemo only)			X Adults	X Adults Children: birth to age 17	X Adults Children ≥ 2	X Adults Child-ren ≥ 2	X Adults Children ≥ 2

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplant; chemo, chemotherapy; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; PBPC, peripheral blood progenitor cell;

[a] "Non-myeloid" is not specifically defined in prescribing information. However, this usually means cancers other than myelogenous leukemias (eg, it may reasonably refer to various solid tumors, lymphoma, and non-myeloid leukemias)[86]

Table 2 includes an overview of the available dosage forms and recommended dose for each CSF according to prescribing information. For additional detail such as the duration of use, monitoring, dose adjustments, and strengths of formulations available, see **Appendix A.**

As shown in **Table 2**, the short-acting G-CSFs including filgrastim, filgrastim biosimilars and tbo-filgrastim, and sargramostim require at least daily dosing for their respective indicated uses.[4,13] This contrasts with pegfilgrastim and pegfilgrastim biosimilars which require less frequent dosing (eg, once-per-chemotherapy cycle).[15] Recommended dosing of short-acting G-CSFs is weight-based and sargramostim dosing is usually based on body surface area[3,4,10,11,13]; this contrasts with pegfilgrastim and pegfilgrastim biosimilars, where a single fixed dose (6 mg) is recommended for all patients except for those weighing <45 kg (weight-based doses are recommended for this population).[14-18]

Depending on the indication, filgrastim, filgrastim biosimilars, and sargramostim can be given subcutaneously or intravenously, contingent on the formulation (see **Table 2**).[3,4,10,11] Pegfilgrastim, pegfilgrastim biosimilars, and tbo-filgrastim are administered subcutaneously.[13-18] When given subcutaneously, each product can be self- or caregiver-administered after training on the technique.[3,4,10,11,13-18] For products using weight-based doses, training should ensure patients can accurately measure the dose. Sargramostim is only available in vials,[4] unlike other products with prefilled syringes,[3,10,11,13-18] which might be a consideration when identifying appropriate candidates for self-administration. In children weighing <45 kg, careful instruction and measurement of the pegfilgrastim/pegfilgrastim biosimilar dose is required because the fixed-dose preparation is not available as a graduated syringe for accurate delivery of doses less than 6 mg.[14-18] Filgrastim, filgrastim-sndz, pegfilgrastim, and pegfilgrastim-bmez prefilled syringes contain dry natural rubber and should be avoided in patients with latex allergies.[3,11,14,17] The sargramostim solution (multi-dose vial) contains 1.1% benzyl alcohol which should be avoided during pregnancy and for infants due to the risk of "gasping syndrome".[4] An option for these populations is the lyophilized powder when reconstituted with sterile water without preservatives.[4]

For reducing the risk of febrile neutropenia and/or the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy, the short-acting G-CSFs should be started at least 24 hours after chemotherapy and are typically continued until recovery of the absolute neutrophil count (ANC).[3,10,11,13] The usual duration of filgrastim in pivotal clinical trials was about 11 days.[87] For a majority of short-acting G-CSF products indications, G-CSF is continued until reaching a target ANC recovery or threshold white blood cell (WBC) count.[3,10,11,13] For patients with severe chronic neutropenia disorders, the dose of filgrastim/filgrastim biosimilar is adjusted based on patient response including ANC.[3,10,11] This necessitates laboratory monitoring at baseline and frequently during use.[3,10,11,13] Similarly, sargramostim should not be started within 24 hours of chemotherapy or radiotherapy, and for a majority of indications, the duration of use is dependent on ANC recovery, requiring laboratory monitoring.[4] In contrast, pegfilgrastim and pegfilgrastim biosimilars are given as a fixed dose regardless of ANC recovery, though prescribing information recommends laboratory monitoring during use to check for leukocytosis.[14-17]

A practical advantage of the long-acting G-CSFs is the lack of requirement for daily administration, which may be favored by some patients. Pegfilgrastim (and *not* its biosimilars) also offers the Neulasta Onpro kit, which is an on-body autoinjector (OBI) that can be fitted to a patient's abdomen or back of arm by a healthcare provider, and will deliver the pegfilgrastim dose approximately 27 hours after placement.[14] This is theoretically advantageous as pegfilgrastim for prophylaxis of febrile neutropenia should be

started at least 24 hours after completion of the myelosuppressive chemotherapy; thus, this device could be fitted while the patient is in the clinic for chemotherapy, and scheduled to deliver the dose the next day without the need for the patient to return to the clinic.[14,88] The OBI can *only* be paired with the prefilled pegfilgrastim syringe co-packaged with it, as this syringe is formulated to account for the need for additional liquid to deliver an accurate dose with the OBI.[14] Potential disadvantages of the OBI are that is requires placement with an acrylic adhesive (problematic in sensitive patients), and rarely, the OBI device fails to deliver the subcutaneous dose correctly.[14]

As of 2019, based on US market share estimates, pegfilgrastim is the most commonly used CSF in the US, followed closely by filgrastim; sargramostim encompasses only a small fraction of US market shares (<3%).[89] Among a population of US adult patients who received a long-acting G-CSF in 2018 or 2019, the OBI-pegfilgrastim accounted for 44.9% of the commercial insurance utilization and 52.4% of the Medicare utilization.[90] The most common cancer types among recipients of G-CSFs in this population were breast cancer, lung cancer, and non-Hodgkin's lymphoma.[90]

As of April 2022, none of the CSFs (G-CSFs or GM-CSF) are listed on the Utah Medicaid PDL either as preferred or non-preferred.

Table 2. Overview of Colony-Stimulating Factor Dosing and Administration for FDA-Approved Uses

Generic Name **Brand** and forms (Approval yr, manufacturer)	**FDA-Indicated Population,** **Starting Dose**[a] *Limitations for use*	
Short-acting granulocyte colony-stimulating factors (G-CSF)		
Filgrastim[3] **Neupogen** • Single-dose vial, for IV‡ or subQ use • Single-dose prefilled syringe* for subQ use (1991, Amgen)	Non-myeloid cancer patients receiving myelosuppressive chemo OR AML patients receiving chemo	5 mg/kg/day IV infusion or subQ once daily
	Non-myeloid cancer patients receiving a BMT	10 mg/kg/day IV infusion
	Autologous progenitor cell collection	10 mg/kg/day subQ once daily
	Severe chronic neutropenia in patients with: • Congenital neutropenia • Idiopathic/cyclic neutropenia	 6 mcg/kg subQ twice daily 5 mg/kg subQ once daily
	Acute myelosuppressive radiation syndrome	10 mg/kg subQ once daily

Table 2. Overview of Colony-Stimulating Factor Dosing and Administration for FDA-Approved Uses

Biosimilars to Neupogen **Filgrastim-aafi**[10] **Nivestym** • Single-dose vial for subQ or IV‡ use • Single-dose prefilled syringe for subQ use (2018, Pfizer Inc.) **Filgrastim-ayow**[12] **Releuko** • Single-dose vial‡ for subQ or IV use • Single-dose prefilled syringe for subQ use (2022, Kashiv/Amneal Biosciences)[b] **Filgrastim-sndz**[11] **Zarxio** • Single-dose prefilled syringe* for subQ or IV‡ use (2015, Sandoz Inc.)	Same as Neupogen (except not indicated for treatment of acute myelosuppressive radiation syndrome; *and filgrastim-ayow is also not indicated for mobilization of autologous progenitor cells*) Do NOT directly administer using a prefilled syringe for doses <0.3 mL (180 mcg) due to potential inaccuracy from the needle guard	
Tbo-filgrastim[13] **Granix** • Single-dose vial for subQ use only • Single-dose prefilled syringe for subQ use (2012, Teva Pharmaceuticals)	Non-myeloid cancer patients receiving myelosuppressive chemo (age ≥ 1 month)	5 mg/kg SubQ once daily
Long-acting granulocyte colony-stimulating factors (G-CSF)		
Pegfilgrastim[14] **Neulasta** • Single-dose prefilled syringe* for subQ use • Single-dose prefilled syringe* for on-body injector subQ use (Neulasta Onpro Kit) (2002, Amgen)	Non-myeloid cancer patients receiving myelosuppressive chemo	6 mg subQ once per chemo cycle
	Acute myelosuppressive radiation syndrome	Two 6 mg doses, subQ one week apart
	For weight < 45 kg: • Use smaller, weight-based doses[c] • Do not directly *administer* the prefilled syringe due to potential inaccuracy with volumes <0.6 mL	
	Limitations of use: • Not for blood progenitor cell mobilization for SCT • On-body injection is NOT for acute radiation syndrome and has not been studied in children	
Biosimilars to Neulasta **Pegfilgrastim-jmdb**[15] **Fulphila**	Non-myeloid cancer patients receiving myelosuppressive chemo	6 mg subQ once per chemo cycle
	For weight < 45 kg:	

Table 2. Overview of Colony-Stimulating Factor Dosing and Administration for FDA-Approved Uses

• Single-dose prefilled syringe for subQ use • (2018, Mylan Pharmaceuticals Inc.) **Pegfilgrastim-apgf** **Nyvepria** • Single-dose prefilled syringe for subQ use • (2020, Pfizer Inc.) **Pegfilgrastim-cbqv** **Udenyca** • Single-dose prefilled syringe for subQ use • (2018, Coherus BioSciences) **Pegfilgrastim-bmez** **Ziextenzo** • Single-dose prefilled syringe* for subQ use • (2019, Sandoz Inc.)	• Use smaller, weight-based doses[c] • All pre-filled syringes: do not directly *administer,* due to potential inaccuracy with volumes <0.6 mL	
	Limitations of use: Not for blood progenitor cell mobilization for SCT	
Granulocyte-macrophage colony-stimulating factor (GM-CSF)		
Sargramostim **Leukine** • Single-dose vial of lyophilized powder† for IV or subQ[§] use • Multi-dose vial, solution† for IV or subQ use (1991, Sanofi-Aventis U.S. LLC)	AML patients post chemo (age ≥ 55)	250 mcg/m^2/day IV infusion over 24 hours or subQ once daily
	Autologous progenitor cell collection (adults)	
	After *autologous* bone marrow/progenitor cell transplant for NHL, ALL, or HL (age ≥ 2 years)	• BMT: 250 mcg/m^2/day IV infusion over 2 hours • For PBPC transplant: 250 mcg/m^2/day IV infusion over 24 hours
	After *allogeneic BMT* (age ≥ 2 years)	250 mcg/m^2/day IV infusion over 2 hours
	Treatment of delayed/failed neutrophil recovery after auto/allo BMT (age ≥ 2 years)	
	Acute myelosuppressive radiation syndrome (from birth to adults)	Weight-based[c] subQ dose once daily

Abbreviations: ALL, acute lymphoblastic leukemia; allo, allogeneic; AML, acute myeloid leukemia; ANC, absolute neutrophil count; auto, autologous; BL, baseline; CBC, complete blood count; BMT, bone marrow transplant; chemo, chemotherapy; Gy, gray; HL, Hodgkin's lymphoma; IV, intravenous; max, maximum; mcg, micrograms; mL, milliliter; NHL, non-Hodgkin's lymphoma; PBPC, peripheral blood progenitor cell; SCT, stem cell transplant; subQ, subcutaneous; W, week; WBC, white blood cell; wt, weight; yr, year

[a] This table lists the *general* population, formulation and dose for the FDA-approved uses. **See Appendix A for details regarding the exact indication, doses, and available formulations.**

[b] Filgrastim-ayow was approved in late February 2022 and is expected to become available for use in the third quarter of 2022

[c] Specific doses are provided per body weight range. Consult prescribing information.

* Formulation incorporates latex in the syringe stopper; avoid use in patients with severe allergy to latex

‡ Dilute vial contents according to manufacturer instructions for IV use

Table 2. Overview of Colony-Stimulating Factor Dosing and Administration for FDA-Approved Uses

§ Prescribing information is not clear regarding administration route. We believe the reconstituted lyophilized powder may be administered by IV or subQ route.
† The lyophilized powder should be reconstituted with 1 mL of sterile water or bacteriostatic water. The multi-dose vial contents require dilution for IV use, but can be used directly for subQ use. Do not use the solution for injection (containing 1.1% benzyl alcohol) in neonates/infants/during pregnancy. All products are produced in yeast and are contraindicated in patients with a yeast allergy.

Methods

Systematic Literature Search

A search strategy consisting of keywords and controlled vocabulary (eg, Medical Subject Heading (MeSH) terms) was developed in Ovid-Medline and translated to Embase and Epistemonikos (for SRs only). See **Appendix B** for the complete search strategies. Initial searches were for systematic reviews (SRs). Cochrane search filters for RCTs and independently derived SR filters or filters adapted from a validated filter were employed for Ovid-Medline and Embase; this included an RCT filter from the Cochrane Collaboration Handbook for Ovid-Medline[91], an RCT filter from the Cochrane website for Embase,[92] and a review filter for Ovid-Medline adapted from a filter developed by McMaster University.[93] We excluded conference abstracts in the Embase RCT search. For Epistemonikos, the database-developed filter for "Systematic Review" was used.

The SR searches were performed for the date range of from inception to January 24, 2022 (Ovid-Medline) or February 3, 2022 (Embase and Epistemonikos). Ovid-Medline and Embase were searched for RCTs published between 2014 and approximately February 11, 2022. The date restriction to from 2014 was based on the comprehensive literature search performed for the 2015 American Society of Clinical Oncology (ASCO) guideline (their search was through September 2014),[21] and informed by the results of our SR search. An additional targeted search for a filgrastim biosimilar FDA-approved after our initial search (filgrastim-ayow) was performed in Ovid-Medline and Embase using free text terms for that product.

Websites of the following organizations were searched for relevant studies or clinical practice guidelines:

I. For studies about the medications of interest: Agency for Healthcare Research and Quality (AHRQ) https://www.ahrq.gov/research/findings/evidence-based-reports/search.html; Institute for Clinical and Economic Review (ICER) https://icer.org/
II. For US guidelines addressing FDA-approved indications or off-label uses of interest (see inclusion and exclusion criteria): ASCO (American Society of Clinical Oncology), NCCN (National Comprehensive Cancer Network), ASTCT (American Society for Transplantation and Cellular Therapy), ASH (American Society of Hematology), Children's Oncology Group (COG) endorsed guidelines, the American Society of Pediatric Hematology/Oncology ASPHO), and the Severe Chronic Neutropenia International Registry. See **Appendix C** for a list of guidelines that were screened but not included in this report.
    a. We searched most NCCN guidelines for mention of the CSFs of interest regardless whether the indication is FDA-approved based on selecting titles of interest (ie,

supportive care guidelines, guidelines for special populations, and guidelines for disease states that were not addressed by the hematopoietic growth factors guideline such pediatric cancers and hematologic cancers).

b. We also checked for NCCN recommendations for CSFs in the NCCN Drugs and Biologics Compendium (https://www.nccn.org/compendia-templates/compendia/nccn-compendia).
c. We also performed a literature search for any off-label condition given a level IIa recommendation or designated as level A evidence for use of CSFs by Micromedex. This included 3 conditions, 2 of which are addressed by NCCN guidelines. A search for guidelines addressing the 3rd condition, neonatal sepsis, was performed in UpToDate.

Prescribing information (ie, package inserts) was searched on the FDA website (Drugs@FDA), dailymed.nlm.nih.gov, and/or the drug sponsor's website. Information about the approval status of biosimilar products was searched on the FDA website, and the FDA Purple Book (database of licensed biological products): https://purplebooksearch.fda.gov/. Information about potential off-label uses was searched in the Micromedex database (IBM). The compendia, Lexicomp (Wolter's Kluwer), was searched for information about use of CSFs during pregnancy or lactation.

Screening

An initial screen for inclusion based on titles and abstracts was performed independently by 2 reviewers. Any conflicts between reviewers from title and abstract screening was resolved by consensus. Articles selected for full-text screening based on the consensus of 2 reviewers were reviewed by the lead author for inclusion. **Figure 1** in **Appendix D** shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

Inclusion and Exclusion Criteria

Included studies are systematic reviews (SRs) and/or meta-analyses (MAs) of randomized controlled trials (RCTs) that included a head-to-head comparison for an efficacy outcome between 2 or more of our products of interest. Only studies comparing efficacy for an FDA-approved indication or an off-label indication meeting at least 1 of the following criteria were included: 1) prophylaxis of febrile neutropenia for any oncology patient (eg, including leukemia, and myelodysplastic syndromes); 2) mobilization of progenitor cells for *allogeneic* transplant; 3) treatment of sepsis; or 4) an indication which is an FDA-approved use for at least one of the medications. We included SR evidence with 1 or more RCTs using CSFs not available in the US as long as some of the included RCTs used US-available G-CSFs and those RCTs of US-available products were not already included by another SR. We also considered the G-CSF dose; for SRs, any dose was allowed, but for individual RCTs addressing on-label uses, we selected studies using doses consistent with US-labeling for adults and/or children. One exception to this is for studies of sargramostim where any dose was allowed in light of the paucity of evidence. For studies comparing reference products to their biosimilar, we included SR evidence only, given that these products met the FDA's biosimilarity criteria.

Excluded studies met one or more of the following criteria: 1) review articles that did not report SR methodology, 2) network MAs without any head-to-head (direct) comparison, 3) SRs of phase 2 RCTs only, or phase 2 RCTs when a phase 3 RCT for the same indication is available (we allowed phase 2 RCTs that were in a substantially different population [eg, leukemia instead of solid tumor] or for a different direct comparison and were not 'dose-finding' trials), 5) post-hoc, exploratory or subgroup analyses, 6)

pharmacokinetic-only studies, 7) SR published more than 5 years ago which includes RCTs already included by a newer SR, 8) studies published in a language other than English or Spanish, 9) studies published only as an abstract, and 10) an RCT that we already summarized from an SR.

Disease Overview

Chemotherapy-induced Neutropenia (CIN) and Febrile Neutropenia (FN)

Myelosuppression with resultant impaired hematopoiesis and fewer erythrocytes, platelets, and white blood cells,[94] is a recognized dose-limiting toxicity of some cytotoxic chemotherapies.[95] Examples of antineoplastic drug classes associated with CIN include anthracyclines (eg, doxorubicin),[96] alkylating agents (eg, cyclophosphamide),[96,97] plant-derived alkaloids (eg, docetaxel),[97] topoisomerase II inhibitors (eg, etoposide),[96] and platinating agents (eg, cisplatin).[97] Some immunotherapies such as the monoclonal antibody, rituximab, may also induce neutropenia.[20]

Absolute neutrophil count (ANC), a measurement of neutrophil concentration in the blood, is usually used to track the neutropenic severity. The incidence of severe infection increases proportionally with both the magnitude of neutropenia (often expressed by the 0 to 4 grade rating; 4 being the most severe, with an ANC $<0.5 \times 10^9$/L) and duration of neutropenia.[6] In patients receiving chemotherapy, neutropenia lasting 7 days or longer prior to contracting a blood stream infection, is a risk factor for mortality within 30 days.[98] Neutropenia has deleterious consequences both due to infection-related morbidity and mortality, and the negative implications on the chemotherapy regimen (ie, forcing a delay in therapy and/or a lower dosage than desired for optimal treatment of the cancer).[6] Neutropenic risk is generally highest during cycle 1 of a given chemotherapy regimen.[6] Chemotherapy-induced neutropenia follows an expected trajectory that varies based on patient and treatment factors.[6] The ANC nadir is the point at which neutrophils are at the lowest concentration on this trajectory.[6] G-CSFs modify this trajectory, altering the shape of neutrophil concentration-time curve, increasing the ANC nadir, and reducing the duration of neutropenia.[99] Use of a G-CSF during cycle 1 is generally expected to reduce the incidence and duration of severe neutropenia following cycle 1 and in subsequent cycles.[6]

Febrile neutropenia (FN) is usually defined as shown in **Table 3.** Fever may be the only presenting symptom of an infection in a neutropenic patient.[6] FN is a medical emergency[100] that necessitates prompt triage and treatment with antibiotics.[34] FN requiring hospitalization is a source of morbidity and mortality among cancer patients, and results in significant costs to the healthcare system. In a cohort of adult cancer patients hospitalized for FN between 1995 and 2000, FN led to death among 9.5% of admissions.[7] Similarly in a cohort of children with cancer (aged under 21 years) who were hospitalized with FN between 1995 and 2002, the mortality rate was 3%.[101] Mortality risk varies based on type of infection, comorbidities, type of cancer, and age; the rate may be as high as 50% in patients with multiple major comorbidities.[7] The estimated rate of hospitalization for neutropenia is higher for patients with hematological malignancies, particularly leukemias (~85 hospitalizations per 1000 patients with that cancer type), compared to solid tumors with a high prevalence of treatment with chemotherapy (~5 hospitalizations per 1000 with multiple types of solid tumors).[102] The higher risk of neutropenia with hematologic malignancies is attributed to both the disease itself and the type of required treatment.[6]

Table 3. NCCN Definition of Febrile Neutropenia[a, 20]

- **Oral temperature:** ≥ 38.3°C (single measurement) OR ≥ 38.0°C (for duration ≥ 1h)
  AND
- **Neutropenia:**
  - < 500 neutrophils/µL (often considered *severe neutropenia*) OR
  - < 1000 neutrophil/µL PLUS decrease to ≤ 500 neutrophils/µL expected within next 48h

Abbreviations: C, Celsius; h, hour; NCCN, National Comprehensive Cancer Network
[a] Per the NCCN "Hematopoietic Growth Factors" version 1.2022 guideline, a guideline generally aimed at adults with solid tumors or lymphoma

Universal prophylactic use of G-CSFs for all cancer patients undergoing chemotherapy is not considered cost-effective.[20,103] Today, a risk-based approach is advocated to identify patients with a non-myelogenous malignancy who are most likely to benefit from CSFs.[20,21] This guideline-directed approach recommends *primary prophylaxis* of FN, that is the use of a CSF closely following completion of the first chemotherapy cycle and prior to neutropenia, for those who are at high-risk for CIN or to enable dose-dense chemotherapy.[20,21] *Secondary prophylaxis,* or the prophylactic use of CSFs in the 2nd or later chemotherapy cycles after a neutropenic event is also generally advocated by this targeted approach.[20,21] Primary prophylaxis with G-CSF compared to no G-CSF treatment in patients with malignancies other than leukemia or multiple myeloma and with variable baseline FN risk was shown to significantly reduce FN and infection-related mortality by approximately 46% and 45%, respectively, in a meta-analysis of RCTs.[100] This effect was observed regardless of age, G-CSF used, antibiotic prophylaxis, and use of G-CSFs as secondary prophylaxis in the non-GCSF study arms; however, the efficacy varied by malignancy type.[100] G-CSF primary prophylaxis in adults with solid tumors or lymphoma has also been shown to significantly improve all-cause survival by 8% in a meta-analysis of RCTs, an effect that is attributed to enabling enhanced chemotherapy delivery (eg, higher intensity due to increased dose or frequency).[104]

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a heterogenous type of blood cancer characterized by expansion of immature myeloid precursor cells (leukemia cells are also referred to as "blasts").[105] It is the most common *acute* leukemia among adults,[24] with approximately 20,240 new cases diagnosed in the US in 2021.[106] AML is most common in older adults with the median age at diagnosis of 68 years. In 2021, there were approximately 11,400 deaths among people with AML in the US[106]; between 2011 and 2017, the 5-year survival rate was about 30%.[105] Diagnosis of AML is based on the presence of an excess of blasts (20% or greater) in peripheral blood or bone marrow, or less commonly, based on the presence of certain cytogenetics regardless of blast count percentage.[24,105] There are multiple risk factors for AML including environmental exposures, genetic predisposition, and other exposures including cytotoxic chemotherapies (this may account for up to 20% of AML cases) and radiation used to treat other cancers.[24] People with myelodysplastic syndromes (MDS), a diverse group of myeloid malignancies characterized by cytopenia and bone marrow dysplasia, are at an increased risk for AML.[36] Additionally, patients with a history of MDS (eg, not de novo AML) are less responsive to treatment.[36]

Initial treatment of AML generally includes 2 phases of chemotherapy: induction and consolidation therapy.[24] *Induction therapy* aims to halt the rapid myeloid blast cell expansion, restoring hematopoiesis and inducing blast cell remission.[24,105] *Consolidation therapy*, also referred to as post-remission therapy,

is given after induction therapy with the goal of removing any residual lurking cancer cells to induce a permanent remission.[24,105] Radiation and maintenance chemotherapy are also a possible treatment modalities.[105] In treatment-refractory or relapsed cases, additional chemotherapy or targeted therapy followed by an allogeneic hematopoietic cell transplant may be indicated.[24] The selected treatment depends on the AML subtype, cytogenetic/molecular prognostic markers, treatment history, and other patient factors (eg, age [particularly age ≥ 60], comorbidities, general health status).[24] Prolonged severe neutropenia is common in AML patients receiving induction and consolidation chemotherapy.[107]

Peripheral Blood and Bone Marrow Stem Cell Transplant

Many terms are used to describe the process of extracting cells and later administering them to replace cells. Both peripheral blood stem cell transplant (PBSCT) and bone marrow transplant (BMT) are procedures for replacement of blood-forming cells that differ based on where the progenitor cells are collected (ie, bone marrow versus peripheral blood).[9] Hematopoietic stem cells are precursor cells that develop into red blood cells, platelets, and white blood cells.[108] More generally, the term hematopoietic cell transplant (HCT) refers to the transplant of these cells (originating from the bone marrow, umbilical cord or peripheral blood) and can be used to refer to PBSCT or BMT.[109] An *autologous* transplant is a transplant where the stem cell donor and recipient are the same person, whereas in an *allogeneic* transplant, the stem cells come from someone else, a matched-donor.[9] Generally, CSFs may be used to mobilize progenitor cells in the peripheral blood of donors, or to promote faster recovery of the bone marrow following a HCT for selected conditions.[3,4]

HCTs are a potentially curative therapy for malignant (primarily hematologic cancers) and non-malignant conditions (eg, bone marrow disorders like severe aplastic anemia, congenital disorders like sickle cell disease, or other disorders of the immune system) in adults and children.[8] They may also be used as an adjunctive therapy for treatment of certain solid tumors requiring myeloablative (high-dose) chemotherapy.[30] The option for an autologous versus allogeneic transplant varies by indication. In some cases, individuals may only have the option for a particular type of transplant (see the 2020 guideline from the American Society for Transplantation and Cellular Therapy).[8]

Today, PBSCT is a popular option for HCT,[110] particularly for an autologous transplant, but BMTs still occur, especially for allogeneic transplants.[30,111] According to the Center for International Blood & Marrow Research, the number of annual HCTs in the US has been steadily climbing since the late 1980s. In the US in 2019, over 24,000 HCTs were performed (approximately 14,720 autologous and 9,500 allogeneic HCT). The most common indication for a HCT in 2019 was multiple myeloma and types of lymphoma (comprising 37% of all HCTs); acute leukemia and myelodysplastic disorders were the most common indications for allogeneic HCTs.[111]

Hematopoietic Syndrome of Acute Radiation

Acute radiation syndrome (ARS) is a disorder characterized by symptoms of damage to organs (hematologic, gastrointestinal, and cardiac/neurologic) following exposure to ionizing radiation.[112] Toxicity may occur after exposure to doses between 1-12 Gray (Gy) units as a consequence of radiotherapy, nuclear accidents, or atomic bombs. Hematopoietic toxicity manifests like a bone marrow failure disorder (eg, low white blood cells and platelets and associated symptoms) and typically occurs after radiation exposure in the sternum or pelvic region.[113] After large exposures, death is expected in almost all cases.[113] The dose cutoff for a large exposure varies, with some citing above 8 Gy,[113] and others, up to 12 Gy.[114] Variability in the dose cutoff may be due to the fact that severity also depends on

other factors such as radiation type, form of radiation (eg, particle, gas, etc), location and uniformity (eg, whole or partial-body, etc), and patient factors.[114] Treatment of ARS, caused by radiation exposures between roughly 2-8 Gy, is expected to increase survival by approximately 50%.[113]

Four hematopoietic growth factors, filgrastim, pegfilgrastim, sagramostim and romiplostim (a thrombopoietin receptor agonist that increases platelets)[115] are FDA-indicated for treatment of hematopoietic syndrome of acute radiation (H-ARS) following exposures greater than 2 Gy.[3,4,15,115] Approval for this use is from clinical studies in non-human primates based on FDA rules for potentially lethal conditions that cannot be ethically tested in clinical trials.[114] Animal studies demonstrated a faster recovery of granulocytes with both filgrastim and sagramostim.[114] According to expert opinion these growth factors should be used as an adjunct to supportive care, but the degree of supportive care indicated based on clinical studies varies between products. "Full supportive care" (ie, blood transfusions, antibiotics) is recommended with filgrastim and pegfilgrastim, whereas sargramostim can be used with "minimal supportive care" (ie, fluids, antibiotics).[116]

Severe Chronic Neutropenia Disorders

Severe chronic neutropenia (SCN) is an umbrella term for a group of rare heterogenous disorders characterized by neutropenia. According to the Severe Chronic Neutropenia International Registry (SCNIR), examples of types of SCN include[19]:

I. Congenital neutropenia: Kostmann's syndrome, Cyclic neutropenia, Glucose-6-phosphatase Catalytic Subunit-3 gene (G6PC3)
II. Metabolic disorders that may have neutropenia: Schwachman-Diamond syndrome, Glycogen storage disease, Barth syndrome
III. Immune disorders that may have neutropenia: Myelokathexis/WHIM syndrome, Wiskott-Aldrich syndrome
IV. Acquired neutropenia: idiopathic or autoimmune neutropenia

Congenital neutropenia is an inherited disorder that presents at birth; affected individuals demonstrate mostly undeveloped neutrophils, and display recurrent infections early in life. Cyclic neutropenia is also inherited, and is due to a variable rate of production of cells in the bone marrow. Although patterns are heterogeneous, most individuals fluctuate between times of low neutrophils and normal neutrophil counts, following a 21 day pattern. At times of neutropenia, people with cyclic neutropenia are at increased risk for infections. Idiopathic neutropenia, neutropenia of an unknown cause, is a heterogeneous disorder. Like other neutropenic disorders, affected individuals are at an elevated risk for infection.[19]

We did not find any guidelines aimed at treatment of patients with SCN, although the NCCN guideline on hematopoietic growth factors does mention that G-CSF is an effective treatment and that the only alternative treatment is a hematopoietic stem cell transplant.[20] Likewise, **the handbook for patients from the SCNIR (2017) recommends daily G-CSF as a first-line therapy for most patients with these disorders.** The only potentially curative therapy for SCN is a HCT, which SCNIR recommends for patients who do not respond to standard treatment and patients who develop MDS/leukemia.[19] A concern with chronic use of G-CSFs in patients with SCN disorders is that some of these disorders are predisposed to developing myelodysplasia and leukemia,[20] and that G-CSF may potentiate this risk.[3] However, long-term follow-up of a cohort of SCN patients with almost 3000 patient-years of G-CSF treatment experience suggests development of AML is rare and may not be associated with G-CSF use.[117]

Only filgrastim and its biosimilars are FDA-approved for treatment of SCN (including patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia per prescribing information).[3,10,11] Chronic treatment is required for most people with these disorders to decrease the risk for infection.[19] An RCT of 120 adults and children with SCN (including idiopathic neutropenia, cyclic neutropenia and congenital neutropenia [including patients with Kostmann's syndrome, Schwachman-Diamond syndrome and myelokathexis]) with a baseline absolute neutrophil count (ANC) < 0.5 x 10^9/L demonstrated the superiority of filgrastim (administered subcutaneously daily, dose-adjusted per ANC response[§§]) to standard of care; 90% of patients responded to daily treatment with filgrastim, defined as reaching an ANC ≥ 1.5 x 10^9/mL. A lower incidence of infections, duration of infection events, and antibiotic use were also observed with filgrastim compared to no treatment.[118]

Clinical Practice Guidelines for Use of CSFs

Overview of guideline recommendations

The following sections summarize US guideline recommendations, primarily for on-label uses of colony-stimulating factors (CSFs). Guidelines from the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and American Society for Transplantation and Cellular Therapy (ASTCT) organizations address most FDA-indicated uses except treatment of severe chronic neutropenia disorders. One International guideline from World Health Organization is also included for treatment of acute radiation disorder since it is an authority for this use.[33] In addition, other off-label uses for CSFs as recommended by NCCN are incorporated into this guideline section.

Guideline discussion sections are organized by disorder, treatment modality (eg, hematopoietic cell transplant), or other specific indications (eg, management of immunotherapy side effects or *treatment* of febrile neutropenia or infections in cancer patients). However, these sections are not necessarily mutually exclusive.

Table 4 provides an overview of *most* situations in which an NCCN guideline recommends use of a CSF. We elected to include NCCN recommendations in this overview table since these guidelines touch on all uses for CSFs that are summarized in this guideline section and in most cases, have been updated most recently. Note that this overview is our *best interpretation* of which products are recommended by the NCCN guideline; in many cases, the guideline was not specific about which CSF is recommended. When guidelines specify a particular agent, it is stated in the table; otherwise, if a recommendation did not list a specific product(s), inferences could be made based on combined information from guideline discussion sections and the NCCN Drug and Biologics Compendia.[***] If it was not possible to infer that a particular agent was recommended, we refer more generally to drug class or all CSFs.

As shown by **Table 4,** filgrastim or an FDA-approved filgrastim biosimilar are recommended for nearly all possible indications for CSFs addressed by the NCCN (ie, in the setting of hematology or oncology disorders). One exception is that GM-CSF (eg, sargramostim) is recommended as part of a specific

[§§] Initial doses varied by disorder. For idiopathic neutropenia, 3.45 mcg/kg/day; for cyclic neutropenia, 5.75 mcg/kg/day, and for congenital neutropenia 11.5 mcg/kg/day that was split into twice daily administrations.
[***] The NCCN Drug and Biologics Compendium compiles NCCN guideline-recommended uses for medications. However, it does not address *all possible* uses listed in guidelines (for example, when a guideline generically recommends myeloid growth factors instead of a specific drug). The compendium is a recognized authority for reimbursement by some payors, including the Center for Medicare and Medicaid Services.

chemotherapy regimen for patients with a type of leukemia/lymphoma that transformed to diffuse large B-cell lymphoma.[25] Some guidelines specifically extend filgrastim recommendations to tbo-filgrastim in addition to filgrastim biosimilars, but this approach is not universally adopted across NCCN guidelines. GM-CSF is recommended for the fewest NCCN-addressed uses. Most NCCN guidelines focus on *adults*; the extent to which the NCCN would extend these recommendations to children is unclear. The 2015 ASCO general guideline for use of CSFs addresses children and adults (with a focus on solid tumors/lymphoma), recommends using CSFs in children when it aligns with clinical protocol.[21]

Table 4. Overview of NCCN Guideline Recommendations for G-CSF or GM-CSF Products

Indication	Product that could be used to satisfy the recommendation[a]:					
	FIL	FIL BIO	TBO-FIL	PEG	PEG BIO	SAR
Neutropenic or immunocompromised patients with cancer (most evidence is for adults)						
Adjunct treatment of infection in patients not responding to standard care[34]	**G-CSF[b] or GM-CSF**					
Non-myeloid solid tumors or lymphoma						
Febrile neutropenia (FN) primary prophylaxis in **adults** with non-myeloid cancer receiving high-risk chemo or intermediate risk with ≥ 1 risk factor[20]	✓	✓	✓	✓	✓	
FN secondary prophylaxis in **adults** with non-myeloid cancer with FN in prior cycle (without G-CSF)[20]	✓	✓	✓	✓	✓	
FN treatment in **adults** without prophylaxis and that have risk factors for complications[b,20]	✓	✓	✓			✓
FN treatment in adults with FN already receiving short-acting G-CSF for prophylaxis[20]	✓	✓	✓			
With **chemo regimen I or M** in **adults/children** with *Wilm's tumor*[23]	✓	✓		✓	✓	
Supportive care during chemotherapy for *aggressive mature B-cell lymphoma* in **children**[119]	**"Growth factors"** may be considered per physician preference in light of minimal evidence					
Myeloid disorders and/or leukemia						
***Adults** with* **Acute Myeloid Leukemia**						
Treatment induction combined with specific chemotherapy with age <60 and favorable, intermediate, or poor-risk cytogenetics[24]	✓	✓				
Treatment induction as part of an *alternative* non-anthracycline chemotherapy and age ≥ 60[24]	✓	✓				
Part of **re-induction regimen** in patients with a late relapse[24]	✓	✓				
Treatment induction combined with specific chemotherapy for relapsed/refractory AML[24]	✓	✓				
Supportive care during treatment with venetoclax + HMA + LDAC, in certain circumstances[24]	**"Growth factors" recommended;** but, supportive text mentions **G-CSFs**.					

Table 4. Overview of NCCN Guideline Recommendations for G-CSF or GM-CSF Products

Indication	Product that could be used to satisfy the recommendation[a]: FIL	FIL BIO	TBO-FIL	PEG	PEG BIO	SAR
General supportive care (eg, life-threatening infection)[24]	**"Growth factors"** listed as a primarily non-routine, option. G-CSF/GM-CSF *not* recommended during APL induction therapy.					
Acute Lymphoblastic Leukemia						
Part of the **FLAG-IDA regimen** for relapsed/refractory Ph-negative B-ALL in **adults** and **pediatrics**[35,120]	✓[c]	✓[c]				
Supportive care during myelosuppressive chemotherapy or per-protocol in **adults**[35]	✓[c]	✓[c]				
Treatment of FN in **pediatric** vulnerable populations not responding to other treatments (eg, antibiotics) alone[120]	✓					
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (age group not specified)						
Combined with HyperCVAD + rituximab for treatment of Richter's transformation to diffuse large B-cell lymphoma[25]						✓
Supportive care for drug-induced toxicity[25]	**"Neutrophil growth factors"** for venetoclax-associated neutropenia; **"Growth factors"** for lenalidomide-associated cytopenia					
Chronic Myeloid Leukemia (age group not specified)						
For management of **tyrosine-kinase inhibitor (TKI)-associated toxicities**[26]	**"Myeloid growth factors"** may be used to manage neutropenia and/or thrombocytopenia from specific TKIs					
Hairy Cell Leukemia (age group not specified)						
Part of **treatment** of FN after chemotherapy[121]	✓	✓				
***Adults** with* **Myelodysplastic Syndromes**						
Combined with ESA as initial treatment of symptomatic anemia in patients with lower-risk disease and certain characteristics[36]	✓	✓	✓			
Combined with ESA as after failed ESA monotherapy for treatment of symptomatic anemia in patients with lower-risk disease and certain characteristics[36]	✓	✓	✓			
Part of **treatment** in neutropenic patients with recurrent/resistant infections[36]	✓	✓	✓			✓
***Adults** with* **Myelofibrosis**						
Supportive care if neutropenic with recurrent infections[37]	**G-CSF or GM-CSF** listed as options					
Hematopoietic Cell Transplant						
Mobilization of stem cells in *autologous or allogeneic* **adult** *donors as* **monotherapy**[d,30]	✓	✓	✓			
Mobilization of stem cells in *autologous* **adult** *donors* with chemotherapy w/wo plerixafor[30]	✓	✓	✓			✓
Mobilization of stem cells in *autologous* adult *donors* combined with plerixafor[30]	✓	✓	✓	✓	✓	
Supportive care for post-auto transplant graft function in **adults**[e,f,30]	✓	✓	✓	✓	✓	

Table 4. Overview of NCCN Guideline Recommendations for G-CSF or GM-CSF Products

Indication	Product that could be used to satisfy the recommendation[a]:					
	FIL	FIL BIO	TBO-FIL	PEG	PEG BIO	SAR
Immunotherapy Toxicity						
Supportive care for CAR-T-associated neutropenia with CRS[27]	✓	✓				**NR**
Exposure to Lethal Doses of Radiation						
Treatment of **H-ARS**[20]	✓	✓	✓	✓	✓	✓

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia (an aggressive AML subtype); CAR-T, Chimeric antigen receptor T-Cell; CRS, cytokine release syndrome; ESA, erythropoiesis-stimulating agent; FIL, filgrastim; FIL BIO, filgrastim biosimilar; FLAG-IDA, fludarabine, high-dose cytarabine, idarubicin, and G-CSF; FN, febrile neutropenia; H-ARS, hematopoietic acute radiation syndrome; HCT, hematopoietic cell transplant; HMA, hypomethylating agents; HyperCVAD, cyclophosphamide, vincristine, liposomal daunorubicin, dexamethasone; LDAC, low-dose cytarabine; NCCN, National Comprehensive Cancer Network; NR, (specifically) not recommended; TBO-FIL, tbo-filgrastim; peg, pegfilgrastim; PEG BIO, pegfilgrastim biosimilar; SAR, sargramostim; W/wo, with or without

[a] This is our interpretation of which CSF products are recommended in NCCN guidelines based on direct statements in the guideline recommendation or inferences from guideline discussion and/or recommendations in the NCCN Drug and Biologics compendium. Note that we believe this to represent most NCCN-listed use, but we did need read all NCCN guidelines (see **Appendix C** on the guideline screening process).

[b] Guideline does not state particular products; they do say to refer to the NCCN hematopoietic growth factors guideline. That guideline does not recommend pegfilgrastim for treatment owing to lack of studies.

[c] Guideline states "G-CSF" but supportive evidence cited is for filgrastim.

[d] For allogeneic transplants, donors may also receive filgrastim/filgrastim biosimilar/tbo-filgrastim in combination with plerixafor if initial monotherapy fails

[e] These indications are mentioned in an older 2021 version of an NCCN guideline, but is not yet incorporated into the newest versions of the guideline, perhaps because of recent changes in focus among guidelines

[f] Pegfilgrastim is recommended for only a HCT whereas (tbo-)filgrastim/biosimilars can be used for other types of auto-transplants

CSF use for FN prophylaxis among patients with non-myeloid solid tumors or lymphoma

General guidelines about the use of hematopoietic growth factors from the NCCN (2021) and white blood cell growth factors from the ASCO (2015) are US guidelines with an emphasis on use of CSFs in patients with a malignancy; however, guideline authors list the target population as primarily people receiving chemotherapy for a solid tumor or lymphoma.[20,21] The NCCN CSF guideline targets adults whereas ASCO includes recommendations for children and adults.[20,21] Primarily addressed in this section is GSFs as prophylaxis of febrile neutropenia (FN) and/or as prophylaxis to enable dose-dense chemotherapy. These guidelines also address some other uses (eg, in the setting of hematopoietic cell transplant, or as part of treatment of febrile neutropenia), but this information is discussed in following sections of this report. **Table 5** summarizes recommendations about use of CSFs from these guidelines and 2 additional guidelines from NCCN focused on types of pediatric solid tumors or lymphoma.

Recommended indications for use of CSFs in this population

For adults with solid tumors or lymphoma, the NCCN recommends *primary prophylaxis* with a CSF (NCCN specifies a G-CSF) after chemotherapy regimens at high-risk (~20% or higher incidence) for FN.[20,21] The NCCN also recommends G-CSF *primary prophylaxis* of neutropenia for patients receiving intermediate-risk (10-20% FN incidence) chemotherapy in patients with 1 or more patient-specific risk

factors for developing FN.[20] Examples of patient risk factors for FN include age >65, liver or renal dysfunction, tumor bone marrow involvement, receipt of prior chemotherapy or radiation, recent surgery/wounds, and persistent neutropenia.[20] Similarly, the ASCO recommends considering patient, disease and treatment factors to determine whether a patient's overall FN risk is ≥ 20%, the approximate threshold at which they recommend primary prophylaxis with a CSF.[21] In some cases, other alternatives (eg, reducing the chemotherapy intensity) may be more appropriate, particularly if the intent of the chemotherapy is palliative.[20] The ASCO also recommends CSF primary prophylaxis in patients receiving dose-dense chemotherapy if there is evidence of benefit (eg, increased survival) from well-designed trials, and for patients ≥ 65 years old with diffuse aggressive lymphoma receiving potentially curative chemotherapy.[21]

As *secondary prophylaxis* (ie, before starting 2nd or later chemotherapy cycle), the NCCN recommends G-CSFs in adult patients that developed FN with the chemotherapy regimen in the absence of prophylactic use of a G-CSF, or in patients that did not previously receive G-CSF prophylaxis and whose neutropenia could negatively influence optimal delivery of their chemotherapy.[20] Similarly, the ASCO recommends secondary prophylaxis for patients that developed a neutropenia-related complication in a prior chemotherapy cycle in the absence of a CSF if use of a CSF may meaningfully impact their disease outcome.[21]

Expert guidance recommendations (published in 2017) based on the Delphi-consensus of international experts, including some from the US, address the place in therapy of pegfilgrastim for CIN prophylaxis, apparently for a population as broad as any cancer patient receiving chemotherapy. According to these experts (91% consensus), relative to short-acting G-CSFs like filgrastim, providers may prefer pegfilgrastim for CIN prophylaxis if there is a risk that the short-acting G-CSF would be given for a shorter duration (ie, fewer than 11 days) than that of pivotal trials comparing pegfilgrastim to filgrastim.[69] These experts list a lack of robust RCT evidence showing a negative impact of daily filgrastim with frequent ANC monitoring on patient adherence; but nonetheless based on case reports, they state (100% consensus) that once-per-cycle pegfilgrastim may be preferred to 11-day filgrastim for CIN prophylaxis "Based on the convenience and patient adherence…This is particularly the case in frail or elderly patients."[69]

In general, prophylactic use of CSFs should be *avoided* in patients receiving concomitant chemotherapy and radiation therapy,[21] or used cautiously.[20]

In the only general guideline addressing prophylactic CSF use in pediatrics (primarily with solid tumors/lymphoma), the ASCO generally extends the approach for primary or secondary prophylaxis with CSFs for adults to children.[21] They also acknowledge that use of CSFs by providers will be guided by "clinical protocols."[21]

Additional NCCN guidelines about solid tumors or lymphoma touch on use of CSFs among pediatric patients with aggressive mature B-cell lymphoma and patients with Wilm's tumor (nephroblastoma), which usually occurs in young children.[23] In the management of aggressive mature B-Cell lymphoma (eg, Burkitt lymphoma and diffuse B-cell lymphoma), guideline authors state that providers may use growth factors (no specific product listed) as supportive care during chemotherapy in accordance with their preference, and may especially consider CSF used in conjunction with the COPADM regimen (cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate) that is associated with a high incidence of neutropenia.[119] For Wilm's tumor, filgrastim or an FDA-approved biosimilar, or pegfilgrastim

or FDA-approved biosimilar, are recommended during the myelosuppressive chemotherapy regimens "M" or "I" (this use is recognized by the NCCN Drug and Biologics compendium[122,123]).[23]

Recommendations about particular products or their administration

The NCCN endorses biosimilars of filgrastim or pegfilgrastim as substitutions for the originator products, and tbo-filgrastim is also an option for FN prophylaxis, consistent with its FDA-approved indication.[20] The ASCO considers filgrastim, filgrastim biosimilars (only filgrastim-sndz was available at the time of this publication), pegfilgrastim, and tbo-filgrastim to be effective options for prevention of myelosuppressive chemotherapy-induced neutropenic complications.[21] Regarding selection of a particular product, they report "The choice of agent depends on convenience, cost, and clinical situation" (eg, patient's chemotherapy is given weekly necessitating a particular product). [21] Nevertheless, ASCO guideline authors describe that a meta-analysis of 5 clinical trials found that pegfilgrastim was more effective than filgrastim for preventing febrile neutropenia in adults with a solid tumor or lymphoma receiving a G-CSF for primary prophylaxis.[49] The ASCO considered there to be a lack of evidence to differentiate between the efficacy G-CSFs and GM-CSFs.[21,124] The NCCN does **NOT** recommend sargramostim in the setting of FN prophylaxis in solid tumor patients receiving myelosuppressive chemotherapy.[20]

The ASCO panel prefers the subcutaneous route of administration for filgrastim, tbo-filgrastim, and filgrastim biosimilars.[21] The NCCN favors the subcutaneous route of administration for all CSF products.[20] Prophylactic filgrastim should be administered until neutrophil recovery.[20] Although evidence suggests greater efficacy for pegfilgrastim prophylaxis given 1-3 days after chemotherapy, the ASCO supports administration of pegfilgrastim on the same-day of the last dose of chemotherapy if this is the only feasible way for indicated patients to receive pegfilgrastim as prophylaxis.[21] Reduced doses of pegfilgrastim to minimize side effects (eg, bone pain) is not recommended by the NCCN as pegfilgrastim is only available in a pre-filled syringe with a single-dose for one-patient use.[20] The NCCN does not support use of pegfilgrastim or biosimilars for chemotherapy regimens requiring weekly cycles due to lack of evidence.[20]

Table 5. US Guideline Recommendations for of CSFs, Primarily as Prophylaxis, for Solid Tumors or Lymphoma

Recommendation	(Strength of recommendation, LOE)[a]
National Comprehensive Cancer Network (NCCN), 2021: Hematopoietic Growth Factors, Version 1.2022[20]	
Target population: Adults with solid tumors or lymphoid malignancy, primarily, receiving chemotherapy	
CSFs are recommended in the following situations Prophylaxis	
• G-CSFs[b], for primary prophylaxis of febrile neutropenia (FN), among adults with solid tumors or non-myeloid malignancies that either will be receiving: ○ High-risk chemotherapy (>20% risk of FN) OR ○ Intermediate-risk chemotherapy (10-20% risk of FN), and ≥ 1 risk-factor is present	Category 1 for high-risk prophylaxis; category 2A for others
• G-CSFs[b], for secondary prophylaxis (second or later cycle) of FN in patients with FN or a neutropenic event that impacted their chemotherapy schedule *that did not previously use a G-CSF*	

Table 5. US Guideline Recommendations for of CSFs, Primarily as Prophylaxis, for Solid Tumors or Lymphoma

Recommendation	(Strength of recommendation, LOE)[a]
Statements about dosing and administration of G-CSF for prophylaxis	
• SubQ route preferred for G-CSFs • Supports use of biosimilars when the original product is recommended • Use caution in patients receiving both chemo and radiation	
• Figrastim/tbo-filgrastim/biosimilars (5 mcg/kg): start 1-4 days after chemo completion and continue through ANC nadir recovery	Category 1
• Pegfilgrastim/biosimilars (6 mg): start 1 day after chemo completion preferred (over same day), may be given 3-4 days later. Use of OnPro device is okay. Should be at least 12 days between giving pegfilgrastim and starting next chemo cycle – NOT recommended for every-week chemo regimens.	Category 1
National Comprehensive Cancer Network (NCCN), 2021: Pediatric Aggressive Mature B-Cell Lymphoma, Version 2.2021[119]	
Target population: Pediatric patients with aggressive mature B-cell lymphoma (including Burkitt lymphoma and diffuse B-cell lymphoma)	
Possible uses for CSF (but not part of the NCCN compendia) • *Growth factors* (specific drugs not listed), as supportive care during chemotherapy ○ "There is a high incidence of fever and neutropenia in COPADM cycles." "There is little published data, but growth factors can be used according to patient stability and physician preference"[119]	Category 2A
American Society of Clinical Oncology (ASCO), 2015: Recommendations for the Use of WBC Growth Factors[21]	
Target population: Adult and pediatric patients receiving chemotherapy for a solid tumor or lymphoma **Interventions:** G-CSF or GM-CSF; for chemo-associated febrile neutropenia, receipt of dose-dense chemo, stem cell mobilization for transplant, or acute radiation syndrome.	
CSFs are recommended in the following situations	

• Primary prophylaxis of neutropenic complications for patients receiving:
  ○ Chemotherapy with ≥ 20% risk (based on patient, disease, and chemotherapy factors) of febrile neutropenia OR dose-dense chemotherapy
  ▪ Recommended for dose-dense chemo only when there is supportive efficacy data
  ○ *Consider* use for patients ≥ 65 years with diffuse aggressive lymphoma "…treated with curative chemotherapy (CHOP-R)"[21]
  ▪ Pegfilgrastim was studied in this setting
	(EB: Strong, high)
	
	(EB; BC or lymphoma: Strong, high; UC: intermediate, moderate)
	(EB: Moderate, intermediate)

• Secondary prophylaxis when prior cycle lacked CSF prophylaxis and CSF use may affect the disease outcome (ie, improve survival or another important treatment outcome)	(EB: Strong, high)
Recommendations for Pediatrics	
• Like adults for primary and secondary prophylaxis of neutropenic complications	(EB: Strong, high)

Table 5. US Guideline Recommendations for of CSFs, Primarily as Prophylaxis, for Solid Tumors or Lymphoma

Recommendation	(Strength of recommendation, LOE)[a]
○ Supportive evidence is for G-CSFs	
• To enable dose-dense chemotherapy when that chemotherapy will prolong survival (eg, Ewing sarcoma)	(EB: Strong, high)
National Comprehensive Cancer Network (NCCN), 2021: Wilms Tumor (Nephroblastoma), Version 2.2021[23]	
Target population: Patients with Wilms tumor of favorable histology, a common primary renal tumor *in children*	
Recommended uses for CSF	
• Filgrastim/pegfilgrastim (or a biosimilar) subQ , as supportive care during treatment with chemotherapy regimen M (containing cyclophosphamide and etoposide) or regimen I (containing cyclophosphamide, doxorubicin, and vincristine)	Category 2A

Abbreviations: BC, breast cancer; COPADM, cyclophosphamide + vincristine + prednisone + doxorubicin + methotrexate; CSF, colony stimulating factor; EB, evidence-based recommendation; HCT, hematopoietic cell transplantation; FN, febrile neutropenia; LOE, level of evidence; PBPC, peripheral blood progenitor cells; SCT, stem cell transplant; SubQ, subcutaneous; UC, urothelial cancer; WBC, white blood cells;

[a] See **Appendix E** for definitions from select guideline developers
[b] Reference to a drug class generally refers to all drugs in that class (ie, for G-CSFs, all short-acting or long-acting products including biosimilars).

CSFs for use among patients with myeloid and/or leukemia malignancies

Most recommended uses of CSFs during chemotherapy for myeloid malignancies are off-label except for use during induction or consolidation therapy for AML (for filgrastim or biosimilars),[3,10,11] and in the setting of certain types of hematopoietic cell transplants for GM-CSF.[4] The NCCN developed separate guidelines to address treatment of specific myeloid malignancies (eg, AML, chronic myeloid leukemia [CML], myeloproliferative neoplasms) and other types of leukemia (eg, acute lymphoblastic leukemia [ALL], chronic lymphocytic leukemia [CLL], and hairy cell leukemia [HCL]). G-CSFs may also be used in the management of myelodysplastic syndromes (MDS), a heterogeneous group of bone marrow failure disorders.[36] **Table 6** summarizes recommended/potential uses of CSFs for these disorders according to NCCN (2021 or 2022) or ASCO (2015) guidelines.

NCCN recommends filgrastim or an FDA-approved filgrastim biosimilar as part of the induction regimen for specific chemotherapy regimens for adult AML patients with favorable-, intermediate-, or poor-risk cytogenetics who are less than 60 years old.[24] In patients 60 years of age or older, the NCCN Drug and Biologics Compendium recognizes use of filgrastim or a biosimilar as part of the induction regimen for AML patients receiving a specific non-anthracycline-containing regimen who can receive aggressive chemotherapy.[122] Filgrastim or a biosimilar may also be used as part of the induction chemotherapy regimen for relapsed or refractory cases in certain circumstances.[24] Filgrastim can be used as part of supportive care for neutropenia, usually between cycles starting after cycle 1, of regimens containing venetoclax with hypomethylating agents and low dose cytarabine that carry a risk of prolonged cytopenia after remission, and possibly, in combination with erythropoiesis-stimulating and

thrombopoietin-stimulating agents in patients who refuse a blood transfusion. After remission (ie, during consolidation therapy), use of growth factors including CSFs is not *routinely* recommended by NCCN, but may be considered for supportive care. Growth factors are recommended as an option to reduce the duration of neutropenia during induction (except for patients with acute promyelocytic leukemia [APL], an AML subtype) or consolidation chemotherapy in patients with life-threatening infections.[24] The ASCO guideline for use of WBC growth factors briefly addresses uses of CSFs in children with AML, recommending **against** use of CSFs for *nonrelapsed* AML without an infection given limited evidence showing a lack of impact on risk of FN and mortality from infections.[21]

In the treatment of ALL, for both children and adults, G-CSF (specific agent not specified[†††125]) is recommended by the NCCN as part of the FLAG-IDA (fludarabine, cytarabine, G-CSF, idarubicin) chemotherapy regimen for treatment of a relapsed/refractory ALL subtype (Philadelphia (PL) chromosome-negative B-cell ALL).[35,120] For adults, G-CSFs (specific agent not specified) are recommended as part of supportive care for particular chemotherapy regimens per treatment protocol or if the regimen is myelosuppressive, and for all regimens in older adults or patients with multiple comorbidities.[35] However, the NCCN pediatric ALL guideline does not routinely recommend CSFs; it states that providers may consider their use as supportive primarily in the context of serious infections.[120] Similarly, the ASCO guideline recommends **against** use of CSFs for *nonrelapsed* pediatric ALL without an infection.[21]

For chronic leukemias (CML and CLL/small lymphocytic lymphoma [SLL]), which usually occur in adults,[25,26] CSFs are primarily mentioned by NCCN guidelines as options for management of drug-specific toxicities. In most cases, these guidelines do not specify a specific agent. The NCCN CML guideline recommends "myeloid growth factors" in combination with tyrosine kinase inhibitors bosutinib, dasatinib, niotinib, and ponatinib, and imatinib for management of persistent neutropenia.[26] GM-CSF is listed by NCCN as part of the hyperCVAD (cyclophosphamide, vincristine, liposomal daunorubicin, dexamethasone) plus rituximab regimen for Richter's transformation of CLL/SLL to DLBCL (diffuse large B-cell lymphoma).[25] The NCCN also recommends neutrophil growth factors for venetoclax-associated neutropenia, and growth factors as supportive care for lenalidomide-induced cytopenia in the treatment of CLL/SLL.[25]

NCCN guidelines for HCL and myeloproliferative neoplasms (MPN) recommend considering CSFs for management of severe, systemic therapy-induced febrile neutropenia (HCL) or recurrent infections in neutropenic patients (MPN).[37,121] The HCL guideline is specific to recommend use of filgrastim or a biosimilar.[121] For MPN, NCCN lists G-CSF or GM-CSF as options.[37]

In the management of adults with myelodysplastic syndromes (MDS), the NCCN recommends low-dose filgrastim, tbo-filgrastim, or filgrastim biosimilar as synergistic combined-treatment with erythropoiesis-stimulating agents for treatment of refractory anemia in patients with *lower-risk* MDS with favorable cytogenetics and a serum erythropoietin level ≤ 500 mU/mL. Response to treatment is expected within 6 to 8 weeks. These therapies should be discontinued if these therapies if no response is observed within the expected timeframe. Additionally, while not recommended routinely as prophylaxis, filgrastim, tbo-filgrastim or a filgrastim biosimilar can be considered for recurrent/resistant infections in neutropenic

[†††] Guideline is non-specific, but the NCCN template for FLAG-IDA orders specifies use of filgrastim.

patients with MDS. GM-CSF is also a potential option for recurrent/resistant bacterial infections in neutropenic patients.[36]

Table 6. US Guideline Recommendations for use of CSFs for Myeloid Malignancies and/or Leukemia

Recommendation	(Strength of recommendation, LOE)[a]
National Comprehensive Cancer Network (NCCN), 2021: Acute Myeloid Leukemia, Version 1.2022[24]	
Target population: Adults (≥ 18 years) with AML **Note:** Most CSF recommendations seem to be for filgrastim or an FDA-approved biosimilar (and not for pegfilgrastim or sargramostim) based on the NCCN Drugs & Biologics Compendium[122]	
Recommended uses for CSF	
As part of *induction* regimen, age < 60 years with favorable-risk cytogenetics[c]: • Filgrastim or its biosimilar[d] subQ, in combination with fludarabine, high-dose cytarabine, and idarubicin plus gemtuzumab ozogamicin	Category 2B
As part of *induction* regimen, age < 60 years with intermediate or poor-risk[c]: • Filgrastim or its biosimilar[d] subQ, in combination with fludarabine, high-dose cytarabine, and idarubicin	Category 2B
As part of *induction* regimen for relapsed or refractory cases (aggressive therapy): • Filgrastim or its biosimilar[d] subQ, in combination with cladribine, cytarabine ± mitoxantrone or idarubicin • Filgrastim or its biosimilar[d] subQ, in combination with fludarabine, cytarabine ± mitoxantrone	Category 2A
As supportive therapy during treatment with venetoclax + HMA + LDAC therapy, in certain circumstances: (not part of the NCCN compendia) • May consider G-CSF (filgrastim)[e] use: ○ *After first cycle* (cycle 2+ if remission achieved after cycle 1), for support between cycles OR ○ If indicated for cytopenia, during first cycle when blasts <5% and the chemotherapy regimen is held	Category 2A
As part of *induction* regimen, age ≥ 60 years receiving a specific regimen[f]: • Filgrastim or biosimilar subQ "…as part of an alternative non-anthracycline-containing regimen (eg, FLAG) in candidates for intensive remission induction therapy who exceed anthracycline dose or have cardiac issues but are still able to receive aggressive therapy"[122]	Category 3
As part of a re-induction regimen with same initially successful regimen after a late (≥ 12 months) relapse[f]: • Filgrastim or biosimilar subQ • In most cases, this would be for cytotoxic chemotherapy regimens[122]	Category 2A
Possible use as part of general supportive care[e] (not part of the NCCN compendia): • Option (with ESA and TPO mimetic, all if benefits > risks), for patients who refuse a blood transfusion • Option during induction chemotherapy (in non-APL patients) for patients with a life-threatening infection	Category 2A Category 2A Category 2A

Table 6. US Guideline Recommendations for use of CSFs for Myeloid Malignancies and/or Leukemia

Recommendation	(Strength of recommendation, LOE)[a]
• Option *post-remission (consolidation) therapy*; ensure patients are off GM-CSF or G-CSF for at least 7 days before documenting remission with BM ○ "Growth factors are not routinely recommended…except in life-threatening infections or when signs and symptoms of sepsis are present and the leukemia is believed to be in remission."[24]	Category 2A
CSF not recommended • G-CSF/GM-CSF during induction therapy for APL (aggressive AML subtype)	
American Society of Clinical Oncology (ASCO), 2015: Recommendations for the Use of WBC Growth Factors[21]	
Target population: Adult and pediatric patients receiving chemotherapy for a solid tumor or lymphoma	
Recommendations regarding CSFs in Pediatrics	
• NOT recommended for *nonrelapsed* ALL or AML in absence of infection	(Consensus: Moderate, Intermediate)
National Comprehensive Cancer Network (NCCN), 2022: Acute Lymphoblastic Leukemia, Version 4.2021[35]	
Target population: Not defined, may be focused on adults given separate pediatric ALL guideline	

Possible uses for CSF (but not part of the NCCN compendia)
• G-CSF, as supportive care "for myelosuppressive blocks of therapy or as directed by treatment protocol"[35]
  ○ Type of G-CSF not specified; *filgrastim* was studied in the cited supportive RCT
• G-CSF, as part of the FLAG-IDA regimen (a recommended, but less preferred regimen) for relapsed/refractory Ph-negative B-ALL
  ○ Type of G-CSF not specified
• Growth factor support may be considered as supportive care with tisgenlecleucel (see immunotherapy toxicity guideline)
• Growth factor supportive care is recommended for *all regimens in older adults (≥ 65 years) or patients with numerous comorbidities*
	All category 2A

National Comprehensive Cancer Network (NCCN), 2021: Pediatric Acute Lymphoblastic Leukemia, Version 1.2022[120]	
Target population: Pediatric ALL	
Possible uses for CSF (but not part of the NCCN compendia) • As supportive care: Filgrastim, pegfilgrastim, sargramostim "…are not generally recommended but may be used at the discretion of the health care provider in situations of serious/life-threatening infection in the context of neutropenia"[120] • Filgrastim, in *vulnerable populations* "…with neutropenic fever who are very ill or not responding to antibiotic/antifungal therapy"[120] • G-CSF, as part of the FLAG-IDA regimen for relapsed/refractory Ph-negative ALL	All category 2A
National Comprehensive Cancer Network (NCCN), 2021: Chronic Myeloid Leukemia, Version 2.2022[26]	
Target population: Not defined; most supportive evidence seems to be for adults, as there is minimal evidence to direct use in children	
Possible uses for CSF (but not part of the NCCN compendia) • *Myeloid growth factors* (specific drugs not listed), *to* manage TKI drug-associated toxicities:	All category 2A

Table 6. US Guideline Recommendations for use of CSFs for Myeloid Malignancies and/or Leukemia

Recommendation	(Strength of recommendation, LOE)[a]
○ For persistent neutropenia and thrombocytopenia with bosutinib, dasatinib, nilotinib, and ponatinib ○ For persistent neutropenia with imatinib ▪ Cites study of filgrastim for this use	
National Comprehensive Cancer Network (NCCN), 2021: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2022[25]	
Target population: Not defined; CLL is a common adult leukemia	
Possible uses for CSF (but not part of the NCCN compendia) • Neutrophil growth factors as supportive care for management of venetoclax-induced neutropenia: "Consider the use of neutrophil growth factors for neutropenia according to standard guidelines." • GM-CSF, in combination with HyperCVAD + rituximab (alternating with methotrexate + cytarabine + rituximab) for treatment of Richter's transformation to diffuse large B-cell lymphoma (DLBCL) • Growth factors, as support for cytopenia during treatment with lenalidomide for CLL	All category 2A
National Comprehensive Cancer Network (NCCN), 2021: Hairy Cell Leukemia, Version 1.2022[121]	
Target population: Not defined; for people with hairy cell leukemia	
Possible uses for CSF (but not part of the NCCN compendia) • Neutrophil growth factors (eg, filgrastim or biosimilar) as supportive care for neutropenic fever after systemic treatment. "The use of G-CSF might be considered in patients with severe neutropenic fever following chemotherapy"[121] ○ Cited evidence is for use with *cladribine* treatment	Category 2A
National Comprehensive Cancer Network (NCCN), 2021: Myeloproliferative Neoplasms, Version 2.2021[37]	
Target population: Adults with MPN including myelofibrosis, polycythemia vera, or essential thrombocythemia	
Possible uses for CSF (but not part of the NCCN compendia) • G-CSF or GM-CSF as supportive care for patients with myelofibrosis and "…recurrent infections in patients with neutropenia"[37]; use cautiously in patients with an enlarged spleen	Category 2A
National Comprehensive Cancer Network (NCCN), 2021: Myelodysplastic Syndromes, Version 3.2022[36]	
Target population: Adults with myelodysplastic syndromes (MDS)	
Recommended uses for CSF Treatment of *symptomatic* anemia in patient with lower-risk disease[g]: • Filgrastim, filgrastim biosimilar, or tbo-filgrastim 1-2 µg/kg subQ once or twice weekly, as initial treatment combined with an ESA in patients with *no* del(5q) and ring sideroblasts: ≥ 15% OR ≥ 5% + SF3B1 mutation and serum erythropoietin level ≤ 500 mU/mL ○ Alternatives: luspatercept-aamt (if no response) ○ All treatments ± RBC transfusions/other appropriate support ○ *lower risk disease* = very low to intermediate on IPSS-R scale • Filgrastim, filgrastim biosimilar, or tbo-filgrastim 1-2 µg/kg subQ once or twice weekly, added to ESA, if no response (with adequate iron stores) or loss of	All category 2A

Table 6. US Guideline Recommendations for use of CSFs for Myeloid Malignancies and/or Leukemia

Recommendation	(Strength of recommendation, LOE)[a]
response to ESA monotherapy in patients with *no* del(5q) and ring sideroblasts < 15% OR <5% + SF3B1 mutation and serum erythropoietin level ≤ 500 mU/mL ○ Alternatives: lenalidomide ○ All treatments ± RBC transfusions/other appropriate support ○ *lower risk disease* = very low to intermediate on IPSS-R scale Other potential supportive care uses for filgrastim or biosimilar/tbo-filgrastim: • "**Not** recommended for routine infection prophylaxis"[36] • "Consider use in neutropenic patients with recurrent or resistant infections"[36] (also mentions potential use of GM-CSF for this)	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BW, bone marrow; CLL, chronic lymphocytic leukemia; CSF, colony stimulating factor; ESA, erythropoietin stimulating agent; FLAG-IDA, fludarabine + cytarabine + G-CSF ± idarubicin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HyperCVAD, fractionated cyclophosphamide + vincristine + liposomal daunorubicin + dexamethasone; IPSS-R, Revised International Prognostic Scoring System; LOE, level of evidence; Ph, Philadelphia chromosome; RBC, red blood cell; TKI, tyrosine kinase inhibitor

[a] See **Appendix E** for definitions from select guideline developers
[b] The NCCN Drug & Biologics Compendium provides a list of recommended uses of oncology drugs that is compiled from across all NCCN guidelines. It has been used for reimbursement by some payers, including the Center for Medicare and Medicaid Services. In some cases, the authors of this report noted slight differences from the guidelines, so recommendations are included from both the guideline and compendia. The compendia do not include all recommendations for the use of CSF that are stated in guidelines, which may be related to a lag-time in updating the compendia, or cases where guidelines do not recommend a specific product (eg, "myeloid growth factors" are recommended)
[c] Patients should be "induction eligible" (see definitions in NCCN guideline)
[d] Wording in guideline states "G-CSF," but one initial footnote specifies filgrastim or an FDA-approved biosimilar which matches NCCN guidance from the NCCN drug compendia
[e] Guideline generally recommends "growth factors" but supportive text mentions G-CSFs. The NCCN drug compendia does not list AML-related uses (ie, related to induction, consolidation or for relapsed disease) for pegfilgrastim, so we believe this to refer to filgrastim.
[f] These are recommended uses for filgrastim (with possible substitution by a biosimilar) in the NCCN compendia, but not clearly outlined in the AML guideline.
[g] This is an NCCN compendia recommended use for filgrastim, whereas the other supportive care measures are not listed

CSFs for use in the setting of HCT

CSFs are recommended to mobilize peripheral blood progenitor cells (PBPC) for autologous or allogeneic transplant.[21,30-32] Recommendations for mobilization, primarily for adults, are provided by the NCCN (2021), ASCO (2015) and American Society for Transplantation and Cellular Therapy [ASTCT] (2014). The ASTCT additionally provides recommendations for mobilization in pediatric patients, whereas ASCO does not list a specific age group for their recommendations. Filgrastim (and biosimilars except for filgrastim-ayow[12]) and sargramostim (in adults) are FDA-indicated for mobilization of PBSC for autologous transplant,[3,4,10,11] whereas use is off-label for tbo-filgrastim, and pegfilgrastim or biosimilar.[13-17] Mobilization for allogeneic transplant is an off-label use for all products.[3,4,10,11,13-17]

Recommendations for a particular CSF agent vary based on the type of malignancy/transplant, age group, and background therapy.[126] The NCCN takes the approach of recommending initial treatment options and for treatment after initial failure (see **Table 7** for recommendations after initial failure). The ASCO does not list specific product recommendations or type of transplantation, generally recommending CSFs alone or in combination with other therapies (plerixafor or chemotherapy) for transplant.[126] Plerixafor (Mozobil) is a CXCR4 receptor blocker indicated for use with G-CSF for PBSC mobilization in non-Hodgkin's lymphoma or multiple myeloma patients undergoing an autologous transplant.[127] The NCCN extends any recommendations for filgrastim or pegfilgrastim to their biosimilars (including tbo-filgrastim),[30] although an earlier guideline from the same year acknowledges that there is minimal evidence for long-term outcomes from use of biosimilars in this setting, so providers should monitor patients for complications (this is part of a section that has not been updated yet in the most recent NCCN HCT guideline).[32] The following CSF regimens are recommended by NCCN and ASTCT for use in adults undergoing autologous HCT:

- Filgrastim alone (NCCN and ASTCT),[30,31] or in combination with chemotherapy and/or plerixafor (NCCN)[30]
- Pegfilgrastim monotherapy or combined with chemotherapy (ASTCT); or, pegfilgrastim combined with plerixafor (NCCN)[30]
- Sargramostim in combination with chemotherapy with or without plerixafor (NCCN)[30]

For autologous pediatric donors, like adults but based on a lower level of evidence, ASTCT recommends filgrastim alone or in combination with chemotherapy for plerixafor; and pegfilgrastim only in combination with chemotherapy, unlike the recommendation in adults.[31]

Recommendations differ slightly for mobilization of PBSC for *allogeneic* transplant from NCCN and ASTCT. For adults, filgrastim monotherapy is recommended;[30,31] and ASTCT also prefers this option over alternatives including pegfilgrastim or plerixafor.[31] Sargramostim is not advised as a single agent by ASTCT because it has been shown to be less effective than G-CSF. For allogeneic pediatric donors, ASTCT recommends filgrastim monotherapy.[31]

Another potential use of CSFs in the HCT setting is as part of *supportive care (eg, for faster neutrophil recovery) post-transplantation*.[32] In general, there is a lack of clinical consensus for use in this setting owing to inconclusive data about benefits.[32] Nevertheless, the NCCN recommends that filgrastim or biosimilar, tbo-filgrastim, or pegfilgrastim or biosimilar can be considered as supportive therapy after an *autologous HCT*. Filgrastim, its biosimilar, or tbo-filgrastim are also recommended for other types of autologous transplants (cord blood, or haploidentical).[32] The ASCO similarly recommends CSFs to shorten time with severe neutropenia after an *autologous* HCT and unlike NCCN, they also weakly recommend its use as supportive care for *allogeneic* HCTs, based on lower quality of evidence.[126]

Table 7. US Guideline Recommendations for use of CSFs in Setting of Hematopoietic Cell Transplants

Recommendation	(Strength of recommendation, LOE)[a]
National Comprehensive Cancer Network (NCCN), 2021: Hematopoietic Cell Transplantation, Version 5.2021[b,30]	
Target population: Adults receiving a HCT due to a malignancy – focused on pre-transplant setting (see disease-state specific guidelines for recommendations on who is a transplant candidate)	

Autologous HCT, mobilization of stem cells – initial treatment
• Recommended possible regimens:
  ○ G-CSF monotherapy
  ○ (G-CSF *or* pegfilgrastim) + plerixafor
  ○ (G-CSF *or* GM-CSF) + cyclophosphamide ± plerixafor
	All category 2A

Autologous HCT, mobilization of stem cells – *after G-CSF monotherapy failure*
• Pharmacotherapy options:
  ○ Increase dose or change G-CSF dosing schedule
  ○ Add plerixafor (to G-CSF)
  ○ Change to chemo-mobilization ± plerixafor regimen	

Allogeneic HCT, mobilization of stem cells – initial treatment • G-CSF monotherapy	All category 2A
Allogeneic HCT, mobilization of stem cells – *after G-CSF monotherapy failure* • Add plerixafor (to G-CSF) • Switch to collection from bone marrow	
General notes • For autologous transplant, in some cases combination treatment may be more effective than G-CSF monotherapy • For autologous transplant, G-CSF or GM-CSF combined with cyclophosphamide are considered similarly efficacious • **"G-CSF" is interpreted to mean filgrastim** ○ Tbo-filgrastim or filgrastim biosimilar substitute is okay • For pegfilgrastim, pegfilgrastim biosimilars can be substituted	
National Comprehensive Cancer Network (NCCN), 2021: Hematopoietic Growth Factors, Version 4.2021[c,32]	
Target population: Primarily adults with solid tumor or lymphoid malignancy • This older version of this guideline includes recommendations about use in the setting of HCT that are not part of the HCT guideline (eg, post-transplant uses). It may not be part of the NCCN compendia owing to the newest HCT guideline not yet including post-HCT recommendations.	
Supportive care – post-transplant, for graft function (not part of NCCN compendia): • Post-autologous transplant (HCT, haploidentical or cord blood): filgrastim or biosimilar, or tbo-filgrastim • Post-autologous HCT: pegfilgrastim or biosimilar	Category 2A Category 2A
Society of Clinical Oncology (ASCO), 2015: Recommendations for the Use of WBC Growth Factors[21]	
Target population: Adult and pediatric patients receiving chemotherapy for a solid tumor or lymphoma	

Table 7. US Guideline Recommendations for use of CSFs in Setting of Hematopoietic Cell Transplants

Recommendation	(Strength of recommendation, LOE)[a]
CSFs are recommended in the following situations	
• To mobilize PBPC for transplantation (alone, after chemo, or combined with plerixafor) ○ Combined use with plerixafor studied with G-CSF	(EB: Strong, high)
• After *autologous or allogeneic* SCT, for shorter length of neutropenia	(Autologous – EB: Strong, high; Allogeneic – EB: Weak, weak)
American Society for Blood and Marrow Transplantation[c], 2014: Peripheral Blood Progenitor Cell Mobilization for Autologous and Allogeneic Hematopoietic Cell Transplantation[b,31]	
Target population: Not defined; provides recommendations for adults and pediatric patients, in the setting of peripheral blood progenitor blood cell collection for HCT	
Allogeneic HCT, for peripheral blood cell mobilization	
• Adults, as monotherapy: filgrastim alone is preferred	Grade A
○ Less preferred options:	
▪ pegfilgrastim (less evidence)	Grade B
▪ Plerixafor (insufficient evidence)	Grade C
○ "Not-advised"[31] as a single agent:	
▪ sargramostim (less cells produced versus G-CSF)	Grade B
• Pediatrics, as monotherapy: filgrastim alone is preferred	Grade C
Autologous HCT, for peripheral blood cell mobilization	
• Adults, for CSF-only mobilization:	
○ Filgrastim monotherapy	Grade A
○ Pegfilgrastim monotherapy	Grade C
○ Filgrastim + plerixafor	Grade A
• Adults, for CSF combined with chemotherapy (starting ≥ 24 hours after chemotherapy) for mobilization:	
○ Filgrastim monotherapy	Grade A
○ Pegfilgrastim monotherapy	Grade A
• Pediatrics, for CSF-only mobilization:	
○ Filgrastim monotherapy	Grade C
○ Filgrastim + plerixafor	Grade C
• Pediatrics, for CSF combined with chemotherapy (starting ≥ 24 hours after chemotherapy) for mobilization:	
○ Filgrastim monotherapy	Grade C
○ Pegfilgrastim monotherapy	Grade C
Additional considerations	
• Combined use of CSF with chemotherapy or plerixafor may be preferred for high-risk patients, or in patients with a failed initial mobilization	Grade C
• There is **insufficient data to recommended G-CSF biosimilars** (at time of publication in 2014)	Grade C

Table 7. US Guideline Recommendations for use of CSFs in Setting of Hematopoietic Cell Transplants

Recommendation	(Strength of recommendation, LOE)[a]

Abbreviations: CSF, colony stimulating factor; EB, evidence-based recommendation; G-CSF, granulocyte colony-stimulating factors; HCT, hematopoietic cell transplant; LOE, level of evidence; PBPC, peripheral blood progenitor cells; SCT, stem cell transplant

[a] See **Appendix E** for definitions of recommendations strength/level of evidence from select guidelines
[b] NCCN and ASTCT guidelines provide specific doses and administration procedures (eg, splitting of doses, and/or timing of administration relative to leukapheresis) for use of CSF agents. In general, the total doses of filgrastim are consistent with prescribing information (ie, filgrastim ~10 mcg/kg/day or sargramostim 250 mcg/m^2/day, daily until leukapheresis). Pegfilgrastim is typically used as 6-12 mg as a single dose. Consult the guidelines for details.
[c] Organization is now known as the American Society for Transplantation and Cellular Therapy

CSFs for treatment of hematopoietic acute radiation syndrome

A World Health Organization (WHO) expert panel (2011) recommends considering treatment with either G-CSF or GM-CSF immediately (within 24 hours) after ionizing radiation exposure in the following situations: (1) exposures ≥ 2 Gy, (2) when a large decrease in absolute lymphocytes is observed, or (3) when an absolute neutrophil count <0.5 x 10^9 cells per liter will last for 7 days or longer.[20] The ASCO (2015) is in agreement with this recommendation, provided that the patient is not expected to expire from other catastrophic injuries in the short-term.[21]

Regarding specific product recommendations, the ASCO does not provide specific guidance, but the NCCN states that all agents (ie, filgrastim or its biosimilar, tbo-filgrastim, pegfilgrastim or its biosimilar, and sargramostim) could be used.[20] The WHO expert panel similarly recommends G-CSFs or GM-CSFs, but among G-CSFs may prefer filgrastim over pegfilgrastim since they state "Pegylated G-CSF may be used as an alternative to G-CSF."[33]

Table 8. US Guideline Recommendations for use of CSFs among Patients with Exposure to Lethal Doses of Radiation

Recommendation	(Strength of recommendation, LOE)[a]
National Comprehensive Cancer Network (NCCN), 2021: Hematopoietic Growth Factors, Version 1.2022[20]	
Target population: Adults with solid tumors or lymphoid malignancy, primarily who are receiving chemotherapy	
• Filgrastim or biosimilar, tbo-filgrastim, pegfilgrastim or biosimilar, or sargramostim, for treatment of H-ARS	Category 2A
Society of Clinical Oncology (ASCO), 2015: Recommendations for the Use of WBC Growth Factors[21]	
Target population: Adult and pediatric patients receiving chemotherapy for a solid tumor or lymphoma	
• CSFs or pegylated G-CSFs, after lethal doses of total-body radiotherapy where death is not certain	(Consensus *by others*[b]: Intermediate, Moderate)
World Health Organization Panel Experts[c], 2011: First Global Consensus for Evidence-Based Management of the Hematopoietic Syndrome Resulting from Exposure to Ionizing Radiation[33]	
Target population: Hematopoietic syndrome in the setting of exposure to ionizing radiation	
• G-CSF or GM-CSF to treat H-ARS when ANC <0.500 x 10^9 cells/L	(Strong, B-1a)

Table 8. US Guideline Recommendations for use of CSFs among Patients with Exposure to Lethal Doses of Radiation

Recommendation	(Strength of recommendation, LOE)[a]
• G-CSF or GM-CSF should be considered in the following situations: ○ Radiation exposure ≥ 2 Gy AND/OR ○ Presence of significant lymphocyte count decrease OR ○ Anticipated ANC <0.500 x 10^9 cells/L for ≥ 7 days	Non-graded recommendation within the text

Abbreviations: ANC, absolute neutrophil count; CSF, colony stimulating factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; Gy, Gray; H-ARS, hematopoietic syndrome of acute radiation; LOE, level of evidence

[a] See **Appendix E** for definitions of recommendations strength/level of evidence from select guidelines
[b] From the 2009 World Health Organization expert panel
[c] A panel of experts was gathered by the World Health Organization in 2009 to review evidence and make recommendations for managing exposure to ionizing radiation

CSFs for treatment of immunotherapy or CAR-T toxicities in oncology patients

Chimeric Antigen Receptor (CAR)-T-cell therapy, a modified T-cell immunotherapy, precipitates cytokine release syndrome (CRS) with an estimated incidence of 60 to 90%.[28] Acute (within 3 months) or prolonged cytopenia, including neutropenia, can occur as a side effect of CAR-T.[28] Both ASCO and NCCN guidelines state that treatment with G-CSF (subQ filgrastim or its biosimilar specified by NCCN) may be considered as adjunctive supportive care for oncology patients with neutropenia and CRS due to CAR-T-cell therapy.[27,28] Sargramostim is **not** recommended in the setting of CRS.[27,28] ASCO additionally recommends supportive care with G-CSF (product not specified) for patients with neutropenia lasting >7 days in association with B-cell aplasia or an infection associated with CAR-T treatment.[28] Growth factor support, which could include CSFs among other agents, can be considered for patients with cytopenia(s) associated with CAR-T therapy, in patients without myelodysplastic syndrome.[28]

Immune checkpoint inhibitors, for example immunotherapies targeting cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) or programmed cell death-1 (PD-1), can uncommonly cause aplastic anemia. Aplastic anemia is characterized by cytopenia of multiple cell lines (eg, low neutrophils, platelets, reticulocytes) and hypocellular marrow. Growth factor support is recommended by the ASCO as part of treatment.[29]

Table 9 shows considerations from ASCO and NCCN for use of G-CSFs or more generally, growth factors, for the management of immunotherapy-related toxicities.

Table 9. US Guideline Recommendations for use of CSFs to manage Chimeric Antigen Receptor T-Cell Therapy or Immunotherapy

Recommendation	(Strength of recommendation, LOE)[a]
National Comprehensive Cancer Network (NCCN), 2021: Management of Immunotherapy-Related Toxicities, Version 4.2021[27]	
Target population: Cancer patients experiencing toxicities related to immunotherapy (including checkpoint inhibitors, and CAR-T cell therapy)	
Possible uses for CSF	
• G-CSF[b] subQ as part of supportive care for *neutropenic* patients with grade 1[c] or higher CRS associated with CAR-T therapy ○ GM-CSF is NOT recommended	Category 2A
American Society of Clinical Oncology (ASCO), 2021: Management of Immune-Related Adverse Events in Patients Treated with Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline[28]	
Target population: Adults with cancer who experience adverse events due to immune checkpoint blockade antibodies or steroids	
Possible uses for CSF	
• G-CSF[d] as part of supportive care for *neutropenic* patients with grade 1[b] or higher CRS associated with CAR-T therapy ○ GM-CSF is NOT recommended • G-CSF[d] as part of supportive care for all grades of B-Cell Aplasia, after >7 days of neutropenia associated with CRS • G-CSF[d] as part of supportive care in patients with infections, and after >7 days of neutropenia associated with CRS • Growth factor support as part of supportive care for cytopenia (as long as not for myelodysplastic syndrome)	Not provided; guideline developed based on informal consensus of experts and SR of evidence
American Society of Clinical Oncology (ASCO), 2021: Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update[29]	
Target population: Adults with cancer who experience adverse events due to immune checkpoint blockade antibodies or steroids	
Possible uses for CSFs	
• Growth factors (details not defined) as part of supportive care for immune checkpoint inhibitor therapy-induced mild to severe aplastic anemia	Not provided; guideline developed based on informal consensus of experts and SR of evidence

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; CSF, colony stimulating factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; LOE, level of evidence; SR, systemic review

[a] See **Appendix E** for definitions of recommendations strength/level of evidence from select guidelines
[b] Guideline does not provide an exact definition for G-CSF; based on footnote, it seems to apply to filgrastim or filgrastim biosimilar.
[c] Grade 1 CRS = fever (≥ 38°C) without an attributable cause, and without hypotension or hypoxia
[d] A particular product is not recommended, though guidelines do not recommend use of GM-CSF (ie, sargramostim) in the setting of CRS.

CSFs for treatment of febrile neutropenia or infections in oncology patients

Treatment of febrile neutropenia (FN) is a potential off-label use for CSFs. NCCN (2021) and ASCO (2015) guidelines provide recommendations about when to consider use of CSFs for oncology patients experiencing FN. See **Table 10** for these recommendations. The NCCN guideline for use of hematopoietic growth factors and the ASCO guideline for WBC factors are primarily aimed at patients with solid tumors or lymphoma.[20,21] The NCCN also has a guideline that refers to the indicated oncology population more broadly, not specifying a certain malignancy, in their guideline regarding prevention of infection, where CSFs can be considered.[34]

In general, CSFs are recommended for treatment of FN in oncology patients who are high-risk for poor outcomes.[20,21,34] Examples of risk factors for poor outcomes include profound neutropenia, expected prolonged (>10 days) neutropenia, serious infections (eg, pneumonia, invasive fungal infections), older age (>65 years), sepsis, and a requirement for hospitalization.[20,21] The NCCN panelists for the guideline on the treatment/prevention of infection acknowledge that it is unclear whether G-CSFs are useful for patients who have an established infection, but similarly recommend use of either G-CSF or GM-CSF in neutropenic patients with serious infections.[34] A meta-analysis cited by ASCO suggests that CSFs may not reduce mortality (vs antibiotics alone) but that they may have other benefits (eg, shortening neutropenia duration, reducing use of antibiotics and duration of hospitalization).[21] CSFs are not routinely recommended for adult patients that are neutropenic, but afebrile.[20,21] Treatment with CSFs may be considered in patients with solid tumors/lymphoma receiving radiation, but not chemotherapy, if extended delays due to neutropenia is anticipated.[21]

Most guidelines do not clearly state a preference for a particular product or class of products. Only the NCCN guideline about use of hematopoietic growth factors is specific about their recommendations – for patients with chemotherapy-induced FN and an indication for a CSF, filgrastim or its biosimilar, tbo-filgrastim, or sargramostim can be considered. Pegfilgrastim is **not** recommended because it has only been studied as prophylaxis.[20] Also, there is a lack of evidence to guide treatment of FN with a CSF in patients that received pegfilgrastim prophylactically; in general, the NCCN recommends avoiding use of other CSFs for treatment within 12-14 days of receipt of pegfilgrastim due to its long-acting effects.[20]

Table 10. US Guideline Recommendations for *Treatment* of Febrile Neutropenia or Infection in Oncology Patients

Recommendation	(Strength of recommendation, LOE)[a]
National Comprehensive Cancer Network (NCCN), 2021: Hematopoietic Growth Factors, Version 1.2022[20]	
Target population: Adults with solid tumors or lymphoid malignancy, primarily, receiving chemotherapy	
CSFs are recommended for treatment when:	
• Filgrastim or biosimilar, tbo-filgrastim, or sargramostim: *Consider use* for patients with FN during chemotherapy who did not receive G-CSF prophylaxis and have risk factors for complications of infection ○ Filgrastim or biosimilar, or tbo-filgrastim should be continued in patients that had already started receiving them as prophylaxis	Category 2A
CSFs are NOT recommended for treatment when:	
• Patients with FN during chemotherapy who did not receive G-CSF prophylaxis without risk factors for complications of an infection • Patients with FN during chemotherapy that *already received pegfilgrastim prophylaxis* (in general, there is a lack of data)	Category 2A
National Comprehensive Cancer Network (NCCN), 2021: Prevention and Treatment of Cancer-Related Infections, Version 1.2021[34]	
Target population: *Neutropenic, or immunocompromised (non-neutropenic) patients* with cancer	
• Consider G-CSF or GM-CSF as an adjunctive treatment for an infection in patients that are not responding/worsening, persistently febrile, or have persistent bacteremia (not part of the NCCN compendium[b])	Category 2B
American Society of Clinical Oncology (ASCO), 2015: Recommendations for the Use of WBC Growth Factors[21]	
Target population: Adult and pediatric patients receiving chemotherapy for a solid tumor or lymphoma	
CSFs are recommended for treatment when:	
• *Consider* use as adjunct to antibiotic in patients with *febrile* neutropenia at-risk for infectious complication or with poor prognostic factors	(EB: Strong, high)
• Patients only receiving radiation (NOT chemo) "…if prolonged delays secondary to neutropenia are expected"[21]	(EB: Strong, high)
CSFs are NOT recommended in the following situations	
• Routine use in adults with cancer and *afebrile* neutropenia	(EB: Strong, high)

Abbreviations: CSF, colony stimulating factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; LOE, level of evidence

[a] See **Appendix E** for definitions of recommendations strength/level of evidence from select guidelines
[b] The NCCN compendium for filgrastim, tbo-filgrastim, pegfilgrastim, or sargramostim does not include recommendations from this guideline (possibly because the guideline does not list a specific CSF). However, the compendium does include the recommendations for treatment of FN from the hematopoietic growth factors guideline without specifying the target type of malignancy.[128-131]

Overview of CSF Off-label Uses per Micromedex

Table 11 compiles the recommendations and evidence ratings that Micromedex provides for recognized off-label uses. There are 2 uses that have a 'IIa' recommendation, meaning that the treatment is recommended for most cases. Figrastim has a 'IIa' recommendation for use in leukemia, especially "…as an alternative or adjunct to donor leukocyte infusions in patients with leukemic relapses after allogeneic stem-cell transplantation."[38] Pegfilgrastim has a 'IIa' recommendation for use in the setting of harvesting of peripheral blood stem cells before autologous stem cell transplant (SCT).[39] **Table 6** of the report can be referred to regarding information/recommendations from US guidelines for uses of CSFs in leukemia; see **Table 7** for SCT-related recommendations.

Most off-label uses of CSFs in **Table 11** are with a 'IIb' recommendation, meaning that treatment is recommended for some cases ('IIb' applies to 12 off-label uses for filgrastim and 9 for sargramostim).[38,40] There are 6 off-label uses for which Micromedex recommends **against** CSF use: filgrastim for glycogen storage disease, meningitis, pneumonia, sinusitis, and tuberculosis[38]; and sargramostim for prophylaxis of neonatal healthcare associated infection.[40]

Table 11. Micromedex Recommendations for Recognized Off Label Uses of CSFs

Off-Label Use	Efficacy (age group)	Recommendation† I: Recommended IIa: Recommended in most cases IIb: Recommended for some III: Not Recommended	Strength of Evidence†
Filgrastim[a,38]			
Agranulocytosis, congenital or drug-induced	evidence favors efficacy (adult)	IIb	C
AIDS-neutropenia	evidence favors efficacy (adult)	IIb	B
Aplastic anemia	evidence favors efficacy (adult)	IIb	C
	evidence favors efficacy (pediatric)	IIb	B
Febrile neutropenia, induced by chemotherapy	evidence favors efficacy (adult)	IIb[b]	B
Febrile neutropenia prophylaxis in myeloid malignancies post-BMT	evidence favors efficacy (adult)	IIb[c]	B
Glycogen storage disease	evidence is inconclusive (adult)	**III**	C
Infectious disease prophylaxis	evidence favors efficacy (adult)	IIb	B
Leukemia	evidence favors efficacy (adult)	**IIa[d]**	B
Meningitis	evidence favors efficacy (adult)	**III**	B
Mucositis (following chemotherapy), Prophylaxis	evidence is inconclusive (adult)	IIb	B

Table 11. Micromedex Recommendations for Recognized Off Label Uses of CSFs

Off-Label Use	Efficacy (age group)	Recommendation† I: Recommended IIa: Recommended in most cases IIb: Recommended for some III: Not Recommended	Strength of Evidence†
Myelodysplastic syndromes (for neutropenia or refractory anemia)	evidence favors efficacy (adult)	IIb[d]	B
Neutropenic disorder, renal transplant related	evidence favors efficacy (adult)	IIb	C
Pre-eclampsia-related neutropenia	evidence favors efficacy (pediatric)	IIb	B
Pneumonia	evidence is inconclusive (adult)	**III**	B
Sepsis of the newborn	evidence is inconclusive (pediatric)	IIb	**A**[e]
Schwachman syndrome[f]	evidence is inconclusive (pediatric)	IIb	C
Sinusitis	evidence is inconclusive (adult)	**III**	B
Tuberculosis	evidence is inconclusive (adult)	**III**	C
Pegfilgrastim[g,39]			
Harvesting of peripheral blood stem cells before autologous SCT	evidence favors efficacy (pediatric and adult)	**IIa**[c]	B
Sargramostim[40]			
Crohn's disease	evidence favors efficacy (adult)	IIb	B
Febrile neutropenia in AML post-induction chemotherapy	evidence favors efficacy (pediatric and adult)	IIb	B
Febrile neutropenia prophylaxis in non-myeloid malignancies after myelosuppressive chemotherapy	evidence favors efficacy (pediatric and adult)	IIb[h]	B
Hepatitis B vaccine, response enhancement	evidence is *inconclusive* (adult)	IIb	B
Healthcare associated infectious disease prophylaxis, neonatal	**Ineffective** (pediatric)	**III**	B
HIV infection – neutropenia	evidence favors efficacy (adult)	IIb	C
Melanoma, malignant	evidence favors efficacy (adult)	IIb	B
Pulmonary alveolar proteinosis	evidence favors efficacy (adult)	IIb	B

Table 11. Micromedex Recommendations for Recognized Off Label Uses of CSFs

Off-Label Use	Efficacy (age group)	Recommendation† I: Recommended IIa: Recommended in most cases IIb: Recommended for some III: Not Recommended	Strength of Evidence†
Renal cell carcinoma, metastatic, adjunct	evidence is inconclusive (adult)	IIb	B
Rhinocerebral mucormycosis, adjunct	evidence favors efficacy (adult)	IIb	C

Abbreviations: AIDS, acquired immunodeficiency syndrome; AML, acute myelogenous leukemia; CSFs, colony-stimulating factors; HIV, human immunodeficiency virus; SCT, stem cell transplant; SRMA, systematic review and meta-analysis

†**Strength of evidence**: A) evidence from meta-analyses of homogenous RCT results; or multiple, well-designed RCTs with large patient population; B) based on meta-analyses of conflicting RCTs; small or methodologically flawed RCTs; or nonrandomized studies; C) based on expert opinion or consensus, case reports or case series

[a] For the biosimilars, no off-label indications are listed in their unique monograph, but links to the off-label uses within the originator, filgrastim, monograph are provided. No off-label uses or links are provided in the monograph for Tbo-filgrastim.

[b] Refer to **Table 10** for US guideline recommendations for CSF use in this population

[c] Refer to **Table 7** for US guideline recommendations for CSF use in this population

[d] Refer to **Table 6** for US guideline recommendations for CSF use in this population

[e] Based on information in UptoDate, and completed SRMAs, some cases of neonatal sepsis may benefit from CSF but this is not a routine use of CSFs due to the inconsistent summary effect (by meta-analysis) of CSFs for improvement of mortality in this population.[132-135]

[f] It is unclear why Micromedex classified Schwachman Syndrome to be an off-label use as patients with this disorder were considered among types of congenital neutropenia disorders in the pivotal trial for approval of filgrastim for treatment of severe chronic neutropenia disorders[3,118]

[g] For the biosimilars of pegfilgrastim with suffixes apgf, bmez, cbqv, and jmdb, links to the off-label uses listed in the monograph of the originator pegfilgrastim are provided.

[h] Refer to **Table 5** for US guideline recommendations for CSF use in this population

In addition to the off-label uses listed in **Table 11**, we are also aware of review articles regarding CSFs in the context of the following disease states:

- acute respiratory distress syndrome[136,137]
- amyotrophic lateral sclerosis[138]
- adjunct in assisted reproduction approaches[139-141]
- autoimmune pulmonary alveolar proteinosis[142]
- chemokine storm[143]
- congestive heart failure[144]
- cystic fibrosis[145]
- management of diabetic foot infections[146,147]
- healing of wounds or burns[148-151]
- ischemic cardiomyopathy[152]
- liver failure[153]

- alcoholic hepatitis[154]
- lower limb ischaemia[155]
- Duchenne muscular dystrophy[156]
- mucositis[157-159]
- myocardial infarct or repair after MI[160]
- Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis[161]
- stroke[153,162]
- vocal fold fibrosis[163]

Pharmacology and Pharmacokinetics

Pharmacology

The CSFs are recombinant human proteins that bind to their receptor (G-CSF receptor or GM-CSF receptor), stimulating development and differentiation of myeloid cells from pluripotent precursor stems cells in the bone marrow as well as enhanced functionality of targeted cells.[164] G-CSFs (including pegylated [eg, pegfilgrastim] and non-pegylated [eg, filgrastim] products) and GM-CSF (sargramostim) differ by which myeloid cell lines they stimulate. G-CSFs more selectively stimulate differentiation of neutrophils whereas sargramostim also stimulates creation of macrophages, and myeloid-derived dendritic cells.[1,3,4] The mechanism of action of pegfilgrastim is considered functionally identical to filgrastim.[2] The CSFs also enhance some functions of these immunologic cells,[1] as shown in **Table 12.**

Table 12. Pharmacologic Comparison of Granulocyte Colony-Stimulating Factors

	Proposed Pharmacology
Recombinant G-CSFs Filgrastim (Neupogen) Tbo-filgrastim (Granix) Filgrastim-aafi (Nivestym) Filgrastim-ayow (Releuko) Filgrastim-sndz (Zarxio) Pegfilgrastim (Neulasta) Pegfilgrastim-jmdb (Fulpilla) Pegfilgrastim-apgf (Nyvepria) Pegfilgrastim-cbqv (Udenyca) Pegfilgrastim-bmex (Ziextenzo)	Primarily stimulates production of the following myeloid-derived cells: • Neutrophils and neutrophil progenitors[3] Other functions: • Enhances some mature neutrophil functions: phagocytosis, cytotoxic roles[1]
Recombinant GM-CSF Sargramostim (Leukine)	Stimulates production of the following myeloid-derived cells: • Neutrophils, monocytes/macrophages, dendritic cells; and their progenitors[4] • Megakaryocyte and erythroid progenitors (but cannot fully stimulate maturation to erythrocytes and platelets without other factors)[4] Other functions: • Enhances "chemotactic, anti-fungal, and anti-parasitic activities"[4] of mature neutrophils, monocytes, and eosinophils[1] • Prevention of accumulation of proteins in lung alveoli[1]

Abbreviations: G-CSFs, granulocyte colony-stimulating factors; GM-CSFs, granulocyte-macrophage colony-stimulating factor

Pharmacokinetics

Recombinant G-CSFs are derived from bacteria (*E*. coli)[3,10,11,13-17] whereas sargramostim is produced from yeast.[4] The amino acid sequence of filgrastim,[3] its biosimilars,[10,11] and tbo-filgrastim[13] matches the endogenous human G-CSF except for an added N-terminal methionine; additionally, these proteins are not glycosylated, unlike the human form.[3,10,11,13-17] Pegfilgrastim is formed from filgrastim by the addition of a polyethylene glycol molecule to methionine at the N-terminus.[2]

Like the G-CSFs, the amino acid sequence for sargramostim is similar to endogenous GM-CSF, differing by one amino acid (leucine instead of arginine). Sargramostim is glycosylated like the native protein.[4] Differences in glycosylation is purported to prevent faster degradation of the protein [89] and possibly affects biologic activity and toxicity (this was observed among comparisons of GM-CSF derived from different sources where glycosylation differed).[165]

An overview of pharmacokinetic (PK) information from the prescribing information for G-CSF products is shown in **Table 13.** The PK profile of filgrastim differs from pegfilgrastim. One key difference is that the clearance of pegfilgrastim is primarily neutrophil-mediated whereas filgrastim is cleared both renally and by neutrophils.[2] Neutrophil-mediated clearance means that drug concentrations are dependent on the presence of neutrophils and are expected to remain high when there are few circulating neutrophils, then decrease as the concentration of neutrophils rises.[2] For filgrastim, the additional renal elimination necessitates daily dosing.[2] However for pegfilgrastim, dependence on neutrophils for clearance allows the drug to persist until approximately 14 days or until neutrophil recovery.[166] Sargramostim has a relatively short half-life, requiring daily dosing.[4]

Pharmacokinetics of biosimilars

Biosimilars to filgrastim and biosimilars to pegfilgrastim were FDA-approved as biosimilars,[10,11,15-17] meaning that they have been demonstrated as having no "…clinically meaningful differences in safety, purity, and potency (safety and effectiveness)…" compared to the reference originator product.[5] Biosimilars have the same amino acid sequence as the originator product and proven similarity in terms of purity and bioactivity. Small differences in sites that are not important to the pharmacologic action are allowed. To demonstrate the biosimilar's lack of "clinically meaningful differences," pharmacokinetic, pharmacodynamic, and immunogenicity comparisons to the reference product are generally conducted.[5]

Although tbo-filgrastim is not a US-approved biosimilar to filgrastim, it has demonstrated bioequivalence to filgrastim for pharmacokinetic and pharmacodynamic (changes in absolute neutrophil count) properties after subcutaneous administration in healthy volunteers.[72]

Drug Interactions

Prescribing information for G-CSF products does not list drug-drug interactions.[3,10,11,13-17] The package insert for sargramostim recommends cautious use with other drugs that may cause myeloproliferation (eg, lithium, corticosteroids).[4] It seems prudent to also consider this precaution when using G-CSFs with drugs that may cause neutrophil proliferation. The NCCN advises that bleomycin-induced pulmonary toxicity may be enhanced by G-CSFs.[20] For this reason, avoidance of G-CSFs is recommended in selected commonly used bleomycin-containing regimens (ABVD and Stanford V but not BEACOPP) for the treatment of Hodgkin's lymphoma.[20]

Table 13. Overview of Pharmacokinetics from Prescribing Information

Generic Name (brand)	Selected PK information	Metabolism and Excretion **Renal or hepatic dose adjustment**	Other notes
Short-acting G-CSFs			
Filgrastim[3] (Neupogen) **Filgrastim-aafi**[10] (Nivestym) **Filgrastim-ayow**[12] (Releuko) **Filgrastim-sndz**[11] (Zarxio)	**Time to C_{max}** (SubQ adm): 2 to 8 hours **Elimination $T_{1/2}$** (IV adm): ~3.5 hours; similar half-lives observed with IV or SubQ use **BA** (subQ): 60 to 70%	• Saturable systematic clearance by G-CSF receptors • Renal excretion No dose adjustments reported	**DDIs:** No interactions reported in prescribing information **SP:** Higher concentrations observed in patient with ESRD. Similar PK properties expected between adults and children. **Immunogenicity:** not fully studied; immunogenicity is possible.
Tbo-filgrastim[13] (Granix)	**Median time to C_{max}** (SubQ adm, adults): 4 to 6 hours **Median elimination $T_{1/2}$** (SubQ adm): ~3 to 3.5 hours **BA** (SubQ): 33%	• Saturable systematic clearance by G-CSF receptors (primary) No dose adjustments reported	**DDIs:** No interactions reported in prescribing information **SP:** Similar PK properties expected between adults and children. Not studied in mod-severe renal impairment, or hepatic impairment. **Immunogenicity:** Transient ADA detected (~1.4% patients) with low titers.
Long-acting G-CSFs			
Pegfilgrastim[14] (Neulasta) **Pegfilgrastim-jmdb**[15] (Fulphila) **Pegfilgrastim-apgf**[18] (Nyvepria) **Pegfilgrastim-cbqv**[16] (Udenyca) **Pegfilgrastim-bmez**[17] (Ziextenzo)	**Elimination $T_{1/2}$** (SubQ adm): adults, 15 to 80 hours **Terminal elimination $T_{1/2}$** (SubQ adm): children 0-5 years, 30.1 ± 38.2 hours; children 6 to 11 years, 20.2 ± 11.3 hours; children 12 to 21 years, 21.2 ± 16 hours	• Saturable systematic clearance by binding to neutrophils No dose adjustments reported	**DDIs:** No interactions reported in prescribing information **SP:** Clearance dependent on body weight; higher exposure expected with higher body weight. Similar PK properties with administration by OBI. Renal function did not change PK parameters. **Immunogenicity:** Small proportion of patients (4/521) developed non-neutralizing, ADA with treatment

Table 13. Overview of Pharmacokinetics from Prescribing Information

Generic Name (brand)	Selected PK information	Metabolism and Excretion **Renal or hepatic dose adjustment**	Other notes
GM-CSF			
Sargramostim[4] (Leukine)	**Time to C_{max}:** immediate (IV), 2.5 to 4 hours (SubQ) **Terminal elimination $T_{1/2}$:** mean of 3.84 hours (IV); 1.4 hours (SubQ) **BA** (SubQ): 75% Injectable dosage forms (powder and solution) considered bioequivalent by SubQ route of administration	• Not characterized; expected: catabolism into peptides/amino acids No dose adjustments reported	**DDIs:** avoid use with other myeloproliferative drugs (eg, lithium, corticosteroids) **SP:** Avoid administration of benzyl alcohol-containing products to infants. **Immunogenicity:** Neutralizing ADA may develop with extended use which may affect therapeutic response – use for shortest needed duration (*labeled warning*)

Abbreviations: Ab, antibodies; ADA, antidrug antibodies; Adm, administration; BA, bioavailability; CYP, cytochrome P450; DDI, drug-drug interaction; HI, hepatic impairment; IV, intravenous; OBI, on-body injector; PK, pharmacokinetic; RI, renal impairment; SP, special populations; SS, steady state; SubQ, subcutaneous; $T_{1/2}$, elimination half-life; Q2W, every 2 weeks; W, weeks

Pregnancy and Lactation

In general, there is little human data to guide use of these products during pregnancy. According to *Briggs Drugs in Pregnancy and Lactation* ("Briggs"), filgrastim is considered compatible with use during pregnancy.[41] Filgrastim appears to have the most published in-human data of the G-CSF and GM-CSF products, and may be preferable over pegfilgrastim during pregnancy owing to case reports and/or observational studies supporting its safety.[41] Animal studies of pegfilgrastim and tbo-filgrastim demonstrated some fetal risk when there was also maternal toxicity.[13,167] Briggs et al did not provide information for tbo-filgrastim specifically, but for pegfilgrastim, the information from animal studies in pregnancy was designated as "low-risk."[167] For sargramostim, there is also no human data; animal studies showed increased spontaneous abortions.[4] Because endogenous GM-CSF naturally increases during pregnancy, Briggs et al do not anticipate fetal harm with sargramostim, but they cautiously advise avoiding its use during pregnancy given the lack of information.[168] The manufacturer advises avoiding use of sargramostim formulations containing benzyl alcohol during pregnancy due to an association between benzyl alcohol and gasping syndrome in neonates/infants.[4]

There is also little information to guide use of these products in people who are breastfeeding. Although there is no in-human data for pegfilgrastim or sargramostim, and only limited human data (that do not suggest fetal risk) for filgrastim, Briggs et al determined that their use is "probably compatible" with breastfeeding.[41,167,168] In part this recommendation seems to be due to the fact that therapeutic proteins like these medications would likely be degraded in an infant's stomach if ingested.[41,167] However, the

manufacturer of sagramostim advises avoiding breastfeeding during treatment with sargramostim and for at least 2 weeks after stopping its use.[4]

Table 14 summarizes information from prescribing information and from Briggs et al, about evidence and recommendations for use of these products during pregnancy or lactation.

Table 14. Overview of Pregnancy and Lactation Information from Prescribing Information

Generic Name (brand)	Pregnancy (Briggs Recommendation[a])	Lactation (Briggs Recommendation[a])
Short-acting G-CSFs		
Filgrastim[3] (Neupogen) **Filgrastim-aafi**[10] (Nivestym) **Filgrastim-ayow**[12] (Releuko) **Filgrastim-sndz**[11] (Zarxio)	• No association with adverse fetal or maternal outcomes in limited available observational human studies • Crosses the human placenta • Animal studies do not suggest fetal malformation risk; increased abortions observed in pregnant rabbits receiving supratherapeutic doses ("Compatible – Maternal Benefit >> Embryo-Fetal Risk")[41]	• Present in human milk • Limited case reports do not suggest infant risk (it is probable that oral the filgrastim would be degraded when ingested orally[41]); consider risks vs benefits of use ("Limited human data – Probably Compatible")[41]
Tbo-filgrastim[13] (Granix)	• Insufficient human data • Animal studies of supratherapeutic doses found higher rates of spontaneous abortion and fetal malformations (along with maternal toxicity) • Consider risks vs benefits of use	• No information about human milk
Long-acting G-CSFs		
Pegfilgrastim[14] (Neulasta) **Pegfilgrastim-jmdb**[15] (Fulphila) **Pegfilgrastim-apgf**[18] (Nyvepria) **Pegfilgrastim-cbqv**[16] (Udenyca) **Pegfilgrastim-bmez**[17] (Ziextenzo)	• Insufficient human data • Animal studies of supratherapeutic doses, transient wavy ribs were observed in rats and increased spontaneous abortions and embryo-lethality (along with maternal toxicity) occurred in rabbits ("No human data – Animal Data Suggest Low Risk")[167]	• No information about human milk; consider risks versus benefits of use • Entry into human milk is considered unlikely, and if it did enter, it is probable that is would be broken down in the infant stomach[167] ("No human data – Probably Compatible")[167]

Table 14. Overview of Pregnancy and Lactation Information from Prescribing Information

Generic Name (brand)	Pregnancy (Briggs Recommendation[a])	Lactation (Briggs Recommendation[a])
GM-CSF		
Sargramostim[4] (Leukine)	• Do NOT use formulations containing benzyl alcohol during pregnancy • Insufficient human data • Animal studies of slightly supratherapeutic doses (≥ 1.3x human exposure) demonstrated increased spontaneous abortions in rabbits • Endogenous GM-CSF crosses the placenta[168] ("No human data – No Relevant Animal Data")[168]	• No information about human milk • May be present in human milk given that endogenous GM-CSF is secreted, but it is not expected to be absorbed by infants [168] • Evidence of increased rabbit death • Manufacturer advises not to breastfeed while receiving sargramostim, and for ≥ 2 weeks after stopping sargramostim ("No human data – Probably Compatible")[168]

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; x, times;
[a] From "Briggs Drugs in Pregnancy and Lactation," as reported in the Lexicomp compendium. This resource did not report separate information for tbo-filgrastim, filgrastim biosimilars, or pegfilgrastim biosimilars.

Direct Comparative Evidence

Overview of Direct Comparative Evidence

An overview of the literature search results is shown in **Figure 1** in **Appendix D.** A total of 815 titles/abstracts were screened, and of these, the full text of 71 articles were screened. A total of 14 SRs or SRMAs of RCTs, and 4 additional RCTs, including 2 RCTs about sargramostim that were identified from reviewing references of reviewed full texts. A total of 55 articles were excluded during full text review. See **Appendix F** for a list of excluded studies and reasons for exclusion.

Refer to **Appendix G Table 1** for a comparison of the RCTs of included SRs that focused primarily on use of G-CSFs for prevention of chemotherapy-induced neutropenia (CIN); this includes comparisons between pegfilgrastim and filgrastim, as well as filgrastim or pegfilgrastim versus their respective biosimilars. In addition, **Table 2** and **Table 3** of **Appendix G** include details of these SRs and of additional RCTs not included in the SRs, and a few RCTs identified from SRs of G-CSFs for prophylaxis of CIN which used doses of pegfilgrastim and/or filgrastim consistent with US prescribing information.

The following is an overview of included evidence:

- Three RCTs were identified that addressed sargramostim versus filgrastim, but they are limited based on use of off-label doses and/or for uses that may not reflect typical clinical practice today. Indications in the RCTs included primary prophylaxis of chemotherapy induced neutropenia (CIN), treatment of afebrile neutropenia, and mobilization of peripheral blood stem cells (PBSCs).

- A majority of studies were in the setting of G-CSFs for primary prophylaxis of CIN/febrile neutropenia (FN) [n = 8 SR/SRMAs with approximately 38 RCTs identified among them]
    - Most studies enrolled patients with solid tumors or lymphoma. The most common type of malignancy was breast cancer. One SRMA focused on patients with hematologic malignancies. Other malignancies included among SRMAs include lymphoma (usually Hodgkin's or non-Hodgkin's), non-small cell or small-cell lung cancer, acute myeloid leukemia, and sarcoma.
    - Very few studies were conducted among children or young adults. Only 1 RCT was identified in this population.
    - The number of SRMAs with particular product comparisons are as follows:
        - Pegfilgrastim vs filgrastim (n = 5)
        - Pegfilgrastim vs pegfilgrastim biosimilars (US and non-US) (n = 3)
        - Filgrastim vs filgrastim biosimilars (US and non-US) (n = 4)
        - Filgrastim vs tbo-filgrastim (n = 1 MA; tbo-filgrastim was lumped in as a filgrastim 'biosimilar' in some SRMAs)
        - Filgrastim vs sargramostim (n = 2)
    - The number of supplemental RCTs (ie, RCTs summarized in addition to results from a SR/SRMA) are as follows (recall we only summarized RCTs that used US-recommended products/doses):
        - Pegfilgrastim vs filgrastim (n = 3; 1 in adults with breast cancer patients, 1 in adults with AML, and 1 in children/young adults with sarcomas)
        - Filgrastim vs tbo-filgrastim (n = 3; 1 in adults with breast cancer, 1 in adults with small-cell or non-small cell lung cancer, and 1 in adults with Non-Hodgkin's lymphoma)
- A smaller number of studies were conducted in the setting of G-CSFs for neutrophil recovery following an autologous peripheral blood stem cell transplant (PBSCT) among cancer patients (2 SRs including 6 RCTs)
    - Most of these studies included patients with lymphoma or multiple myeloma. Fewer patients had an acute leukemia or solid tumor.
    - Only 1 RCT of the 6 enrolled pediatric patients, with a median age of 11.5 years
    - All studies compared pegfilgrastim to filgrastim (n = 2 SRs including 6 applicable RCTs)
- A smaller number of studies were conducted among patients receiving a G-CSF for mobilization of PBSCs before autologous transplant
    - One SRMA including 6 RCTs of patients with various tumor types
        - All RCTs compared filgrastim to pegfilgrastim, primarily in adults
    - 1 additional RCT compared filgrastim and tbo-filgrastim among adults with lymphoma or multiple myeloma

An observation about the included SR/SRMAs, primarily among patients with a solid tumor or lymphoma malignancy receiving a G-CSF for prophylaxis of chemotherapy-induced/febrile neutropenia, is that they often included heterogenous G-CSF products (eg, pooling biosimilar pegfilgrastim or unknown long-acting G-CSF into the "pegfilgrastim" group; we will use the term 'similar' to refer to products where this occurs), variable G-CSF doses (eg, weight-based doses for pegfilgrastim or fixed-doses for filgrastim), and at times, different durations of G-CSF use or different timing of initiation of the G-CSF relative to completion of chemotherapy. The impact of these complex factors on MA results is unknown,

particularly as there seems to be a lack of consensus in the literature. For example, while some weight-based doses of pegfilgrastim (eg, 100 mcg/kg) project similar or higher exposure and achievement of a similar absolute neutrophil count (ANC) response as the fixed-dose of 6 mg in adults; lower doses (eg, 60 mcg/kg) and much lower doses (30 mcg/kg) project a slightly lower or much lower ANC response, respectively.[2] Yet, slightly lower doses (eg, 60 mcg/kg or 3.6 fixed-dose) of pegfilgrastim may reach relatively similar results for duration of severe neutropenia after G-CSF CIN prophylaxis for some patients.[169,170] Duration of use of filgrastim may also be important for optimal results as prophylaxis of CIN/FN. Pivotal trials comparing pegfilgrastim and filgrastim averaged a filgrastim duration of 11 days, and at least some data supports suboptimal outcomes when shorter durations are used.[69] A recent open-label trial reported noninferiority of filgrastim 5 day duration to filgrastim 7-10 day duration, suggesting shorter filgrastim durations may be effective in some populations; however, the 5 day regimen was not compared to an 11 day duration of filgrastim.[171]

Timing of G-CSF initiation relative to other factors may also influence efficacy and/or safety outcomes. For example, a non-randomized study of pegfilgrastim 6 mg/cycle for CIN prophylaxis administered at 24 vs 72 vs 96 hours after chemotherapy in breast cancer patients observed greater rates of severe cytopenia in the 24 hour arm, and the highest rates of early or late leukocytosis in the 24 and 96 hours arms respectively, leading authors to conclude that 72 hour pegfilgrastim administration is optimal for these safety measures.[172] Although, some retrospective observational studies suggest similar outcomes might be achieved with same-day versus next-day administration in some cancer populations.[173,174] Timing of G-CSF initiation for mobilization for PBSCs may also impact the mobilization rate. For example, 1 RCT reported a significantly higher mobilization success rate in the pegfilgrastim arm which started 7 days after cyclophosphamide chemo-mobilization compared to pegfilgrastim which started 3 days after, despite equivalent doses and adjustment for a few other factors.[175]

Overall, owing to aforementioned heterogeneity, we cannot conclude that the results from the SRMAs are generalizable to the exact products available in the US and at doses/regimens used in the US.

Summary of Included Evidence (see additional sections below for more detail)

Filgrastim (or similar short-acting G-CSF) vs pegfilgrastim (or similar long-acting G-CSF):

Prophylaxis of CIN/FN in patients with primarily non-myeloid malignancies: Five SRMAs that include between 7-16 RCTs each compared subQ pegfilgrastim (or a similar long-acting G-CSF) at various doses to subQ filgrastim (or a similar short-acting G-CSF) at various doses, primarily among adults with solid tumors or lymphoma.[44-48] Overall, these studies suggest that a once-per chemotherapy cycle dose of pegfilgrastim is at least as effective and possibility superior to daily doses of filgrastim (given for variable durations, but a majority of the included RCTs averaged at least 7 doses[47] if not 10-11[49,50]) for reducing the incidence of febrile neutropenia.[44-48] The 5 SRMAs were inconsistent regarding the statistical superiority of pegfilgrastim over filgrastim for FN prevention, although the direction of the pooled effect was consistent, favoring pegfilgrastim.[44-48] A statistically significant benefit favoring either treatment was not observed for any other efficacy outcomes reported by the MAs, including incidence of severe (eg, grade 3 or grade 4) neutropenia[44-46] and time to ANC recovery.[45,46] The comparative safety profile from MA of RCTs between pegfilgrastim (or a similar long-acting G-CSF) and filgrastim (or a similar short-acting G-CSF) supports that both G-CSFs carry similar risks of common AEs (ie, bone pain, or myalgia).[44-46] One RCT of the US-recommended doses of pegfilgrastim and filgrastim in adults with

breast cancer reported a numerically higher rate of severe bone pain in the filgrastim versus pegfilgrastim arm.[51]

Prophylaxis of CIN/FN in patients with AML: One phase 2 RCT compared filgrastim 5 mcg/kg/day subQ (continued until ANC recovery) to pegfilgrastim 6 mg/cycle subQ during both induction and consolidation chemotherapy with a high-risk of FN in adult AML patients with primarily intermediate-risk cytogenetics. Pegfilgrastim was similarly effective to filgrastim for the primary outcome of time to ANC recovery from severe neutropenia during both induction and consolidation therapy. Details about the safety profile were underreported, but filgrastim and pegfilgrastim exhibited a similar safety profile in terms of treatment-related AEs and discontinuations due to AEs.[52]

Neutrophil recovery support after autologous peripheral blood stem cell transplant (PBSCT): Two SRs[55,56] identified 6 RCTs comparing pegfilgrastim (6 mg[176-180] or 100 mcg/kg in children,[43] single-dose) to daily filgrastim (primarily 5 mcg/kg, 1 trial used fixed-weight stratum-based doses ranging from 300 mcg to 780 mcg[178]) given until ANC recovery (range of approximately 7-12 days), both given subcutaneously starting between 1-5 days after autologous PBSCT.[43,176-180] Most of the included patients were adults (5 trials),[176-180] and 1 trial included children with a median age of 11.5 years.[43] The type of malignancy varied across these studies; generally, a majority of patients had lymphoma or multiple myeloma,[176-180] or less commonly, acute leukemia or various solid tumors.[43,179,180] All RCTs either failed to show a difference[176,177] or demonstrated noninferior efficacy[43,178,179] of pegfilgrastim compared to filgrastim for their varying primary outcomes, including FN duration,[176] duration of severe neutropenia,[177,179] time to neutrophil[180] or polymorphonuclear engraftment,[43] and time to neutrophil recovery.[178] In the only blinded trial, a higher proportion of filgrastim-treated than pegfilgrastim-treated patients met ANC recovery criteria for discontinuation of G-CSF support; however, they failed to observe any differences in neutropenic sequalae between study arms.[180] Although little detail was specified, both pegfilgrastim and filgrastim were generally considered similarly safe,[176-180] including in the study among pediatric patients.[43]

Mobilization of peripheral blood stem cells: One SRMA of 6 RCTs[53] and 1 additional RCT[54] compared subQ filgrastim to pegfilgrastim. The 6 RCTs were among patients with various types of malignancies including adults with solid tumors, lymphoma, myeloma, leukemia, or unknown, and pediatric/young adult patients with sarcoma, requiring an autologous HCT[53] and the additional RCT was among adults with multiple myeloma.[54] Studied G-CSF doses and timing of administration (when after chemotherapy) were heterogeneous, generally aligning with guideline-recommended doses for pegfilgrastim (ie, 6 to 12 mg one-time, but some used weight-based doses) whereas some studies used a lower filgrastim dose (5 mcg/kg/day) instead of the recommended 10 mcg/kg/day.[53] The cumulative low or very low quality evidence suggests that a single dose of pegfilgrastim is probably comparable to daily filgrastim for achieving successful mobilization (ie, collecting the target number of CD34+ by apheresis) when given after chemotherapy mobilization (2 RCTs),[53] and for the median quantity of CD34+ cells mobilized when given as monotherapy for mobilization (1 RCT)[54] or when given after chemotherapy mobilization (3 RCTs).[53] A safety-focused MA based on 2-3 RCTs suggests similar tolerability between pegfilgrastim and filgrastim with respect to total incidence of bone pain, back pain, and arthralgia.[53]

Filgrastim vs filgrastim biosimilars (or similar product): One SR and 3 SRMAs suggest that US-approved filgrastim biosimilars (or similar non-US products) exhibit comparable efficacy to filgrastim with respect to the duration of severe neutropenia (SN),[44,46,57,58] and prevention of FN[44,46,57] in patients

with cancer receiving chemotherapy. US-available filgrastim biosimilar RCT evidence for prophylaxis of neutropenia after chemotherapy in adult breast cancer patients, including 1 RCT of filgrastim-aafi (Nivestym)[181] and 2 RCTs,[182,183] plus 1 pooled RCT safety analysis of filgrastim-sndz (Zarxio),[184] reported overall similar AEs between the biosimilar and originator filgrastim based on the dose of 5 mcg/kg/day subQ. One RCT compared intravenous filgrastim to intravenous filgrastim-sndz, both dosed as 10 mcg/kg/day for a median of 8 days, finding a comparable mean number of mobilized PBSC collected from adults with hematologic malignancies undergoing autologous PBSCT.[60] The safety profile was also similar in this population. The evidence does not suggest a difference in development of neutralizing antibodies when switching between filgrastim and filgrastim-sndz.[185] No studies reported use of the newest filgrastim biosimilar, filgrastim-ayow.

Pegfilgrastim vs pegfilgrastim biosimilars (or similar product): Three SRMAs of RCTs suggest that US-approved pegfilgrastim biosimilars (or similar non-US products) are similarly efficacious with respect to the duration of SN after cycle 1 of myelosuppressive chemotherapy[57,58] or incidence of SN,[59] prevention of febrile neutropenia after cycle 1 of chemotherapy,[57,59] and time to ANC recovery after cycle 1 of chemotherapy.[57] US-available pegfilgrastim biosimilar RCT evidence of prophylaxis of neutropenia after chemotherapy in adult breast cancer patients, including 1 RCT with filgrastim-jmdb (Fulphila)[186] and 2 RCTs with filgrastim-bmez (Ziextenzo),[187,188] reported overall similar AEs between the biosimilar pegfilgrastim and originator pegfilgrastim based on a dose of 6 mg single subQ dose once per chemotherapy cycle. No neutralizing antibodies developed during these US-available biosimilar studies.[186-188] No RCTs of the two other pegfilgrastim biosimilars, pegfilgrastim-gbqv (Udenyca) and pegfilgrastim-apgf (Nyvepria) were included among the SRs.

Filgrastim vs tbo-filgrastim: Three phase 3 RCTs[63-65] and 1 phase 2 RCT[62] compared these CSFs in adult patients, at doses consistent with prescribing information. The three phase 3 RCTs evaluated comparability of the treatments (filgrastim or tbo-filgrastim 5 mcg/kg/day until ANC recovery or for a minimum of 5 days to a maximum of 14 days) for primary prophylaxis of CIN during chemotherapy cycle 1 and included patients receiving myelosuppressive chemotherapy with either breast cancer, lung cancer, or NHL.[63-65] Duration of severe neutropenia (ANC $<0.5 \times 10^9$/L) was similar between study arms in each study,[63-65] and statistically equivalent (within ± 1 day) in the study among breast cancer patients powered to measure this outcome.[63] A MA pooling these 3 trials demonstrated that filgrastim and tbo-filgrastim are similarly effective at preventing FN during cycle 1 of chemotherapy regardless of the myelotoxic potential of the chemotherapy regimen.[61] A phase 2 trial compared filgrastim and tbo-filgrastim (both at doses of 10 mcg/kg/day x 5 days in combination with co-mobilizer plerixafor on day 4) for mobilization of CD34+ cells for autologous HCT. Treatment with either medication resulted in a similar mean number of collected CD34+ cells/kg after apheresis (per authors, this met the threshold for noninferiority) and most patients achieved the target number of collected cells within 1 apheresis procedure. Similar transplant-related outcomes (eg, time to engraftment) occurred in both arms.[62]

Overall, the safety profile between filgrastim and tbo-filgrastim was similar in the setting of solid tumor or lymphoma patients receiving CSF prophylaxis after chemotherapy,[63-65] and in multiple myeloma or lymphoma patients receiving CSF for mobilization of stem cells for autologous transplant.[62] In the trial among breast cancer patients, the overall incidence of AE was higher with filgrastim than tbo-filgrastim (39.7% vs 25.7%)[63]; however, sufficient information to evaluate if this was the case in other studies was not reported by the other trials.

Filgrastim vs sargramostim: Three RCTs compared these CSFs in adult patients.[66-68] It is important to keep in mind that these trials may have limited generalizability to clinical practice owing to use of doses that do not match current prescribing information or guideline-recommended doses, or due to use of these products in non-routine settings. Comparative RCTs suggest filgrastim (7 mg/kg/day subQ) and sargramostim (193 mg/m^2/day subQ)[‡‡‡] may be similarly tolerable for CIN prophylaxis (possibly at higher than standard filgrastim dose, and below standard sargramostim dose)[66] and similarly effective and tolerable (at standard doses of filgrastim and sargramostim) for treatment of *afebrile* neutropenia in adult cancer patients.[67] For mobilization of progenitor cells in the setting of autologous transplant following a chemo-mobilization regimen, filgrastim treatment yielded a higher median number of cells than sargramostim with fewer apheresis procedures.[68] However, the difference in mobilized cells was not significant in a 1 out of 2 total chemo-mobilization subgroups,[68] suggesting that relative efficacy may depend on the type of chemo-mobilization regimen.

Filgrastim versus pegfilgrastim

Primary Prophylaxis of CIN in Patients with Non-myeloid Malignancies

SRMA assessment of pegfilgrastim (or a similar long-acting G-CSF [PEGb]) vs filgrastim (or a similar short-acting G-CSF [FILb])

Five SRMAs published within the past 5 years that include between 7-16 RCTs each compared PEGb at various doses to FILb at various doses, usually given subcutaneously, for primary prophylaxis of CIN, generally in adults with solid tumors or lymphoma.[44-48] **Table 15** highlights some details from these studies. **Overall, these studies suggest that a once-per chemotherapy cycle dose of a PEGb is at least as effective and possibility superior to daily doses of a FILb (given for variable durations, but majority of the included RCTs averaged at least 7 doses[47] if not 10-11[49,50]) *for reducing the incidence of febrile neutropenia*.** The SRMAs did not classify the baseline FN risk level of chemotherapy regimens among included RCTs; however, other SRs including 6 (earlier RCTs published between 2002 and 2008[51,52,170,189-191]) of the 20 possible RCTs classified the risk as moderate to severe,[50,192] and exceeding the threshold of 20% risk of FN to receive primary G-CSF prophylaxis.[20] Filgrastim- and pegfilgrastim-based products performed similarly for other efficacy outcomes assessed by SRMAs, including incidence of severe (eg, grade 3 or grade 4) neutropenia[44-46] and time to ANC recovery.[45,46] The comparative safety profile assessed by MA supports that short-acting and long-acting G-CSFs carry similar risks of common adverse events (ie, bone pain, or myalgia).[44-46]

[‡‡‡] These are the published doses by investigators, but we wonder if they meant micrograms instead of milligrams. The recommended dose of filgrastim for prophylaxis is 5 mcg/kg/day and sagramostim is usually given at a dose of 250 mcg/m^2/day.

Table 15. Overview of SRMA Efficacy Evidence Comparing Filgrastim to Pegfilgrastim for CIN Prophylaxis

			Efficacy Results from Direct MA	
Author, Year Study design	Population (maximum number of RCTs)	Dose of FIL and PEG[a]	FN Incidence	Select Other Efficacy Outcomes
Rastogi et al 2021[44] SRMA	Adults with solid tumors or lymphoma (9 RCTs)	FIL: 5 mcg/kg/day, or 50 to 100 mcg/m^2/day PEG: 30 – 100 mcg/kg/day or 3 mg – 6 mg/cycle	RR (95% CI), PEG vs FIL: 0.90 (0.67 to 1.12); (I^2 = 52%, P = 0.42)	RR (95% CI), PEG vs FIL: Severe neutropenia: 0.95 (0.81 to 1.12); (I^2 = 39.6%, P = 0.55)
Mohseni et al 2020[45] SRMA	Adults with solid tumors or lymphoma (11 RCTs)	FIL: 3.6 to 6 mg/cycle, or 100 mcg/kg/cycle PEG: 50 to 100 mcg/m^2/day or 5 mcg/kg/day	RR (95% CI), PEG vs FIL: *After cycle 1:* 0.88 [0.66 to 1.16]; (I^2 = 0%, P = 0.35) *All cycles:* 0.76 [0.51 to 1.13]; (I^2 = 4%, P = 0.18)	RR (95% CI), PEG vs FIL: Severe neutropenia: 0.98 (0.91 to 1.06); (I^2 = 39.6%, P = 0.55) Time to ANC recovery: *After cycle 1 (MD):* –0.03 [–0.34 to 0.29]; (I^2 = 0%, P = 0.87)
Wang et al 2019[46] SRMA and SRNMA	Any cancer patients (mostly adult solid tumor or lymphoma, but also children with sarcoma and adults with AML) (16 RCTs)	FIL: 5 mcg/kg/day (most); 1: 300 mcg/day PEG: 30 to 300 mcg/kg/cycle (100 mcg/kg/cycle was most common), 3.6 mg – 6 mg/cycle	OR (95% CI), FIL vs PEG: *Within 2 weeks after chemotherapy:* **1.46 (1.07 to 1.99);** (I^2 = 8%)	OR (95% CI), FIL vs PEG: Severe neutropenia: 1.07 [0.90 to 1.27]; (I^2 = 0%)
Cornes et al 2018[47] SRMA	Adults with non-myeloid cancer, or AML (10 RCTs)	FIL: 300 mcg daily, or 100 mcg/m^2/day, or 5 mcg/kg/day PEG: 60 mcg/kg to 120 mcg/kg single dose or 3.6 to 6 mg per cycle	RR (95% CI), PEG vs FIL: 0.86 [0.68 to 1.10]; (I^2 = 0%, P = 0.226)	
Bond et al 2018[48] SRMA and SRNMA	Adults with solid tumors or lymphoma (7 RCTs)	FIL: 5 mcg/kg/day (most common), or 100 mcg/m^2 (one study) PEG: 3.6 or 6 mg/cycle, or 100 mcg/kg/cycle (most common)	RR (95% CI), FIL vs PEG: **1.54 (1.03 to 2.29)**; (I^2 = 0%, **P = 0.04**)	RR (95% CI), FIL vs PEG: Severe neutropenia 1.01 [0.93 to 1.10]; (I^2 = 0%, P = 0.83) Time to ANC recovery: MD: *0.*28 [–0.10 to 0.67]; (I^2 = 39%, P = 0.15)

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; CI, confidence interval; CIN, chemotherapy-induced neutropenia; FIL, filgrastim; FN, febrile neutropenia; MA, meta-analysis; MD, mean difference; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio; SRMA, systematic review and meta-analysis; SRNMA, systematic review and network meta-analysis;

[a] **Studies may have included US filgrastim or pegfilgrastim products, or in some cases, a non-US biosimilar or nonbiosimilar to the originator products. Most SRMAs describe filgrastim as the originator product and point out some differences in the pegfilgrastim products; however, some individual RCTs mention non-US product origins.**

As shown in **Table 15** and elaborated in **Appendix G,** the included SRMAs are inconsistent with respect to the statistical significance of the comparison between PEGb and FILb for the incidence of FN; 2 MA of RCTs (by **Wang et al 2019[46] and Bond et al 2018[48]**) found PEGb to be superior, while the 3 other MAs (by **Rastogi et al 2019,[44] Mohseni et al 2020,[45] and Cornes et al 2018[47]**) failed to demonstrate superiority of pegfilgrastim over filgrastim for this outcome. Although the they are inconsistent with regard statistical significance, the *point estimate* (pooled risk ratio or odds ratio) for each MA favors PEGb over FILb. We are aware of 4 other SRMAs of RCTs published more than 5 years ago (between 2007 and 2015) which included a mix of RCTs included in the more recent SRMAs.[49,50,193,194] Three of 4 older SRs found a significant benefit favoring pegfilgrastim-based products over filgrastim-based products for the incidence of FN.[49,50,193,194]

The reason for a difference in the statistical significance for the outcome of FN in these SRMAs is unclear; it is likely complex and may be multi-factorial. Examples of possible reasons include differences in the outcome definition (eg, pooled FN risk across all chemotherapy cycles versus only cycle 1), differences in the outcome calculation (eg, RR versus OR), different included RCTs, heterogeneity of included G-CSF products and dosing, heterogeneity in timing of G-CSF start or duration, and other heterogeneity among included patients. **Appendix G Table 1** shows a comparison of included RCTs among the 5 SRMAs comparing filgrastim and pegfilgrastim. Of the 2 SRMAs that did show a significant benefit favoring pegfilgrastim, Wang et al 2019 included the largest number of RCTs including 6 RCTs not included by any of the other SRMAs[46]; and Bond et al 2018 included the fewest number of RCTs.[48] Wang et al did include at least 1 RCT with possible issues; for example, one study lacked true randomization between the G-CSF study arms (randomization was at the level of the number of chemotherapy regimen cycles), and started the G-CSFs at different times (pegfilgrastim was started on day 2 whereas filgrastim was started on day 5 after chemotherapy)[195] which might favor pegfilgrastim.[166]

RCT assessment of US filgrastim vs US pegfilgrastim

None of the identified SRMAs or older SRMAs exclusively included RCTs with US pegfilgrastim or filgrastim, or doses consistent with US prescribing information. Thus we further extracted data for 3 of the RCTs which used US-available products at FDA-labeled CIN prophylactic doses. (See **Appendix G Table 3).** Results from one of these trials (Sierra et al 2008) was conducted in AML patients and is summarized in the next section regarding AML.[52] Results of the 2 RCTs concluded among patients with non-myeloid malignancies are summarized in the following bullets:

- **Green et al 2003** conducted a phase 3, randomized, double-blind, double-dummy, noninferiority trial among adults with breast cancer who received chemotherapy with a high-risk (~30%) of FN. Patients were randomized to filgrastim 5 mcg/kg/day subQ (n =75) continued until ANC recovery (a median of 10-11 injections, varying by cycle number, were achieved) or pegfilgrastim 6 mg subQ once per chemotherapy cycle, both started about 24 hours after chemotherapy. **Noninferiority between filgrastim and pegfilgrastim was established** for the primary endpoint

of the mean duration of grade 4 neutropenia after chemotherapy cycle 1 based on the upper bound for the confidence interval of the difference between arms being less than 1 day; the mean duration in filgrastim arm was 1.6 days compared to 1.8 days in the pegfilgrastim arm (mean difference of 0.23 days; 95%CI –0.15 to 0.63). The incidence of FN in cycle 1 was 9% in the pegfilgrastim arm and 15% in the filgrastim arm. For the overall incidence of FN in any cycle, there was not a statistically significant difference between the G-CSF treatment arms; the incidence was 13% with filgrastim compared to 20% with pegfilgrastim (difference –7%, 95%CI –19% to 5%). Numerically more patients receiving pegfilgrastim were hospitalized compared to filgrastim, 31% vs 18%. **With filgrastim, there was a numerically higher rate of severe bone pain relative to the pegfilgrastim arm, at 1% vs 8%**, respectively; however, the rate of overall bone pain was similar, with 42% filgrastim-treated vs 37% of pegfilgrastim-treated patients reported this adverse event (AE). **The safety profile was overall similar (ie, rate of any drug-related AE) between treatment arms**, and most of the AE were considered mild.[51]

- **Fox et al 2009** conducted a randomized, open-label trial among **children and young adults** (age <26 years; age range was 3.8 to 25.8 years) newly diagnosed with a sarcoma that did not involve the bone marrow. Patients received 6 cycles of 1 type of chemotherapy (V_3DC) and 9 cycles of another type (IE). Patients were randomized to filgrastim (n = 17) 5 mcg/kg/day subQ continued until ANC recovery (mean of 10-13 injections were received) or pegfilgrastim (n = 17) 100 mcg/kg single-dose per chemotherapy cycle subQ.[42] (100 mcg/kg is roughly equivalent to the recommended pegfilgrastim dose for children weighing <45 kg in US prescribing information).[14] Filgrastim or pegfilgrastim prophylaxis was started at roughly the same time after chemotherapy, with filgrastim started about 24 hours after and pegfilgrastim 24-36 hours after. **The study failed to find a significant difference between pegfilgrastim and filgrastim** for the primary outcome of mean duration of severe neutropenia (calculated separated for V_3DC and IE cycles), although not all of the randomized patients were included in this analysis, increasing the risk of bias. The mean duration of severe neutropenia for pegfilgrastim versus filgrastim in the V_3DC and IE cycles respectively were 5.5 vs 6 days (P = 0.76) and 1.5 vs 3.75 days (P=0.11). Numerically more hospitalizations with grade 3 fever and neutropenia during cycles 1-4 occurred in the filgrastim (47% of cycles) versus pegfilgrastim arm (29% cycles). **The safety profile in terms of occurrence of mucositis, bone pain, and increases in hepatic transaminases was similar between the filgrastim- and pegfilgrastim-treated patients**.[42]

Primary Prophylaxis of CIN in Patients with Acute Myelogenous Leukemia (AML)

One randomized, double-blind and double-dummy, multicenter phase 2 trial by **Sierra et al 2008** compared pegfilgrastim (US originator product) 6 mg given once per cycle subcutaneously (n = 42) to filgrastim (US originator product) 5 mcg/kg/day subcutaneously (n = 41), continued until post-nadir ANC recovery (median number of doses 13-16).[52] Both G-CSFs were started 24 hours after idarubicin + cytarabine chemotherapy; G-CSF was given during induction cycle 1 and during consolidation in patients meeting criteria for receipt of consolidation.[52] Included patients were adults with a majority of patients having AML with intermediate-risk cytogenetics.[52] Of note, use of this regimen in AML patients has been considered to carry a high (ie, incidence ≥ 40%) risk of FN.[192] For the primary outcome of time to recovery (2 consecutive ANC values ≥ 0.5 x 10^9/L) from severe neutropenia (ANC <0.5 x 10^9/L) **during the first induction cycle, pegfilgrastim and filgrastim exhibited similar benefits** with the median time being 22 days in both arms (95% CI for the difference, –1.9 to 1.9 days).[52] **Similar benefits between treatment**

arms were observed on the time to ANC recovery during consolidation.[52] The incidence of FN during induction therapy was 81% in the pegfilgrastim arm versus 88% in the filgrastim arm.[52] **Although this study was not a noninferiority trial, authors considered the difference in time to ANC recovery to be less than the minimum clinically important difference of about 2-3 days**.[52] One factor that could have impacted the analysis of this study is that it was stopped early due to a calculation error favoring one of the arms. However, authors believe they were adequately powered to detect any differences in the primary outcome regardless.[52]

The relative safety profile was not well-characterized by this trial. Overall, a similar proportion of patients in both arms experienced treatment-related AE. Authors describe that the types of AE where characteristic of the AML population and similar between treatment groups, but additional detail was not reported.[52]

Mobilization of Peripheral Blood Stem Cells

One SRMA by **Kuan et al 2017[53]** and an RCT by **Skopec et al 2017[54]** that was not among studies included by Kuan et al, compared pegfilgrastim to filgrastim[§§§] for mobilization of peripheral blood stem cells (PBSCs). Kuan et al included 6 RCTs comparing pegfilgrastim and filgrastim in the setting of autologous HCT among cancer patients including unreported type, children/young adults with sarcomas, or adults with lymphoma/myeloma/acute leukemia, solid tumors unspecified, NHL, or non-small cell lung cancer.[53] Both filgrastim and pegfilgrastim were given subcutaneously in these studies, but the doses used and timing of administration relative to chemotherapy was variable; filgrastim was given daily as weight-based doses (5 to 10 mcg/kg/d until apheresis or reaching ANC target) and pegfilgrastim was given as a single fixed-dose (6 mg, 12 mg, or 18 mg) or weight-based single doses (30 to 100 mcg/kg).[53] In all RCTs included by Kuan et al except for one, the G-CSFs were combined with chemotherapy for mobilization.[53] This contrasts with the RCT by Skopec et al which gave G-CSF monotherapy (filgrastim 10 mcg/kg subQ vs pegfilgrastim 12 mg one time subQ) for mobilization, and was conducted among adult multiple myeloma patients awaiting autologous HCT.[54] **Low quality of evidence by the MA of only 2 RCTs demonstrated a similar rate of successful CD34+ mobilization (defined as achievement of collected CD34+ cells ≥ 2 x 10^6/kg) between pegfilgrastim 6 mg single-dose and filgrastim 5 mcg/kg/day (RR 0.87, 95%CI 0.67 to 1.11).[53]** Skopec et al reported on the median number of collected PBSCs, finding a similar median number of collected cells with either medication.[54] This is congruent with very low quality findings from 3 RCTs included by Kuan et al that reported a similar quantity of CD34+ cells between G-CSF groups (all at doses of pegfilgrastim 6 mg vs filgrastim 5 mcg/kg/day).[53] Trials reporting on other efficacy outcomes, considered to be very low quality of evidence, including number of apheresis procedures, peak peripheral blood CD34+ cells and time to neutrophil and platelet engraftment (after HCT) generally reported similar results between filgrastim- and pegfilgrastim-mobilized arms.[53] Skopec et al also reported on neutrophil and platelet engraftment after transplant, finding somewhat similar results between arms, but that slightly numerically favor filgrastim by a median of approximately 2-3 days.[54] Of note, a statistical analysis is lacking for this comparison and even if it had been performed, it would be limited by the lack of power. Overall, the Skopec et al study was limited by a relatively small size (about 20 patients per study arm) and failed to report a power analysis;

[§§§] Kuan et al describe these agents as pegfilgrastim and filgrastim; however, among the 6 included RCTs, 2 do not describe the origins of the products to verify that they are US products and the other 4 suggest use of the US originator products. Skopec et al describe use of pegfilgrastim and filgrastim, but do not specify the product origin.

additionally, it lacked details to assess risk of bias due to blinding or allocation concealment, and it was conducted at a single-site outside of the US which may minimize generalizability.[54]

With respect to safety, the pooled risk of bone pain, back, and arthralgia which included 2-3 RCTs each (one of which used a non-pegfilgrastim long-acting G-CSF among the pegfilgrastim arm) failed to demonstrate a difference between pegfilgrastim and filgrastim for these safety events.[53] Skopec et al included few details about toxicity, only describing that neither grade 3 or 4 adverse events nor leukocytosis (>100 x 10^6/L) occurred in either the filgrastim or pegfilgrastim arm.[54]

Neutrophil Recovery Support after an Autologous HCT

Two SRs by **Busca et al 2018**[55]and **Ziakas et al 2012**[56] *primarily* included studies of G-CSFs for neutrophil support following an autologous PBSCT, mostly among patients with hematologic malignancies including lymphoma and multiple myeloma, or less commonly, solid tumors. Between these SRs, 6 RCTs were included,[43,176-180] 2 of which were phase 3 trials.[43,180] One of the phase 3 trials used a double-dummy approach, giving a matched placebo to mask the filgrastim versus pegfilgrastim arms.[180] Most of the RCTs included adults,[176-180] but 1 RCT included pediatric patients with a median age of 11.5 years.[43] All RCTs compared subcutaneous pegfilgrastim and filgrastim[****]; most studies used a single dose of 6 mg pegfilgrastim (except the pediatric trial used 100 mcg/kg dose with a max of 6 mg[43]), and daily 5 mcg/kg filgrastim,[176,177,179,180] except for 1 trial that dosed filgrastim as fixed-dose based on weight-strata (eg, 300 mcg for weight <60 kg), with a dose range of 300 mcg/day to 780 mcg/day.[178] The start time after the PBSC transfusion varied; 3 trials started both G-CSFs 1 day after transplant,[178-180] while another started 3 days after[43] and another 5 days after.[176] One study started filgrastim 5 days after transplant whereas pegfilgrastim was started 1 day after transplant.[177] In general, filgrastim was continued in all study arms until ANC recovery/neutrophil engraftment, though the exact definition of this endpoint varied slightly across studies.[43,176-180] The median duration of filgrastim varied between 7 days and 12 days[43,176,178,179]; 1 study did not report these details,[177] and the remaining trial reported a mean of 12 injections in both arms (the placebo-controlled trial).[180]

Overall, the results from the 6 trials support **similar efficacy between a single dose of pegfilgrastim and daily doses of filgrastim**, both as supportive care after autologous PBSCT in patients with variable types of malignancy, for their respective primary efficacy outcomes. This includes a similar mean duration of FN (3.07 vs 3.29 days),[176] duration of severe neutropenia (5 vs 6 days),[177] and time to neutrophil engraftment (12 days in both arms)[180] for pegfilgrastim versus filgrastim, respectively. Additionally, noninferiority of pegfilgrastim to filgrastim was established for time to polymorphonuclear leukocyte engraftment (10.44 vs 10.48 days) among children,[43] duration of severe neutropenia (6.20 vs 5.97 days),[179] and time to neutrophil recovery (10.75 vs 11.53 days[179] and 9.3 vs 9.8 days).[178] Most trials also reported similar efficacy for secondary outcomes such as incidence and duration of fever,[43,178,179], duration of hospitalization,[177,179,180] and time to platelet engraftment.[43,176] One exception was the trial by Martino et al, which favored pegfilgrastim for duration of fever and risk of FN; however, this trial started pegfilgrastim earlier than filgrastim, which could explain benefits favoring pegfilgrastim.[177] In the only double-blinded trial, although pegfilgrastim single-dose and filgrastim (mean of 12 injections) were similar for most efficacy measures including the primary outcome, one numeric difference noted by authors was that more patients in the filgrastim arm met the target for discontinuation of CSF support

[****] SR authors describe the agents as filgrastim and pegfilgrastim. Half of included RCTs suggest use of either US- or European-produced originator products, but details of product origin was not reported by the other trials.

(either ANC of 5.0 x 10^9/L x 3 days, or 10 x 10^9/L 1 day) than pegfilgrastim, 95% vs 44%; this corresponded to a significantly higher number of doses to reach this endpoint, a median of 25 in the pegfilgrastim arm vs 13 in the filgrastim arm.[180] Authors pointed out that this did not seem to translate to differences in neutropenia-related sequelae, and that a higher ANC in the filgrastim group (observed for days 12-16 post-transplant) could be due to relatively lower levels of pegfilgrastim, in light of the neutrophil-mediated clearance occurring as the ANC recovered.[180]

Regarding safety, overall, when details were given, the trials reported a similar safety profile between pegfilgrastim and filgrastim. Two trials reported a lack of grade 3 or 4 drug-related toxicity in either arm.[176,180] Several trials reported that the most common AEs were considered to be related to the chemotherapy and transplant itself.[176-178] For example, the most common events in both arms in 1 trial that included this detail were neutropenia, thrombopenia, febrile neutropenia, infection, and anemia.[178] Among trials reporting about bone or musculoskeletal (MSK) pain, 1 study reported severe MSK pain with pegfilgrastim and no cases with filgrastim[178]; the other trial reported the proportion of treated patients with mild to moderate bone pain as 10% in the pegfilgrastim arm and 12% in the filgrastim arm.[177] A few trials reported on rates of mucositis, in 1 trial, severe mucositis occurred in 25% of patients in the pegfilgrastim arm and 20% of the filgrastim arm[176]; in another trial, 51% of filgrastim-treated and 60% of pegfilgrastim-treated patients experienced severe mucositis.[179] Five trials reported information about deaths.[43,176-178,180] Most trials reported a similar number of deaths in both treatment arms and that the deaths were not considered related to the study drugs.[43,176,178,180] One possible exception is a trial that reported 1 death in each study arm, but did not comment on any relationship to the study drugs; the death in filgrastim arm 20 days after PBSCT was due to “cardiac toxicity” and the death in the pegfilgrastim arm 30 days after PBSCT was due to hemorrhagic stroke.[177] The study in pediatric patients reported similar high tolerability of both study drugs, and denied any deaths related to toxicity within 100 days of transplant.[43]

Filgrastim versus filgrastim biosimilars

Two SRs[58,185] and 3 SRMAs[44,46,57] of RCTs compared filgrastim to a filgrastim biosimilar for the prophylaxis of chemotherapy induced neutropenia. Of note, the SRMAs also included studies of comparable agents lacking approval as a biosimilar in the US, primarily for tbo-filgrastim versus filgrastim (up to 3 RCTs) and 1 RCT for a product not available in the US (Hegg et al 2016).[44,46,57] Among included RCTs, 4 studies comparing filgrastim to filgrastim-sndz (Zarxio),[60,182,183] including 1 study which was primarily a pooled safety analysis,[184] and 1 RCT comparing filgrastim to filgrastim-aafi (Nivestym) were included.[181] All included RCTs of FDA approved biosimilars were conducted in adult patients with breast cancer except for 1 RCT comparing filgrastim to filgrastim-sndz for mobilization of PBSCs for autologous PBSCT in adult patients primarily with hematologic malignancies (eg, multiple myeloma, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma).[60] See **Appendix G Table 1** for a comparison of the studies included in each SR/SRMA.

The SRs and SRMAs suggest filgrastim biosimilars (or similar products) are similarly efficacious to filgrastim with respect to the duration of severe neutropenia (SN) after myelosuppressive chemotherapy (the primary outcome for comparable efficacy in most studies[181,182])[44,57] and prevention of febrile neutropenia (primary outcome for 1 RCT[183]).[44,46,57] With respect to safety, filgrastim and filgrastim-aafi at equivalent doses (5 mcg/kg/day) exhibited an overall similar AE profile; although the proportion of patients with bone pain and skeletal muscle pain was numerically higher with filgrastim vs filgrastim-aafi, 26.2% vs 16.8% and 41% vs 32.6%, respectively.[181] A similar proportion of serious AEs and severe

AEs occurred between filgrastim and filgrastim-aafi treatment arms.[181] In a pooled analysis of 2 studies comparing equivalent doses (5 mcg/kg/day) of filgrastim and filgrastim-sndz, an overall similar AE profile was exhibited with respect to total treatment-emergent AEs, drug-related AEs, and serious drug-related AEs.[184] A numerically higher frequency of bone pain occurred in the pooled filgrastim arm (15%) vs filgrastim-sndz (5.8%).[184] **The evidence does not suggest a difference in immunologic response based on development of neutralizing antibodies when switching between filgrastim and filgrastim-sndz**.[185]

Manko et al 2014 found comparable efficacy for mobilization of PBSCs between filgrastim and filgrastim-sndz (both at an *intravenous* dose of 10 mcg/kg/day for a median of 8 days), 9.1 x 10^6 vs 9.4 x 10^6 CD34+ cells/kg, with a comparable number of apheresis procedures (median of 1 for both groups). The safety profile with respect to occurrence of bone pain, nausea/vomiting, diarrhea, and neutropenic fever was similar between groups.[60]

Pegfilgrastim versus pegfilgrastim biosimilars

Three SRMAs of RCTs[46,57,58] compared pegfilgrastim to a pegfilgrastim biosimilar for the prophylaxis of chemotherapy induced neutropenia. Among these SRMAs, 9 RCTs were included; however, only 3 RCTs specified that they were US-available pegfilgrastim biosimilars, including 2 studies of pegfilgrastim-bmez (Ziextenzo)[187,188] and 1 study of pegfllgrastim-jmdb (Fulphila).[186,196] No identified SRs included an RCT comparing the other US pegfilgrastim biosimilars, pegfilgrastim-gbqv (Udenyca) or pegfilgrastim-apgf (Nyvepria). The three RCTs including US-available pegfilgrastim biosimilars were conducted among adult breast cancer patients [186-188,196]; whereas 2 included SRMAs allowed studies comparing pegfilgrastim products among patients with any type of cancer.[57,59] See **Appendix G Table 1** for a comparison of the studies included in each SR/SRMA.

The SRMAs suggest pegfilgrastim biosimilars (or similar products) are similarly efficacious to pegfilgrastim with respect to the duration of SN after cycle 1 of myelosuppressive chemotherapy[57,58] or incidence of SN,[59] prevention of febrile neutropenia after cycle 1 of chemotherapy[57,59] and time to ANC recovery after cycle 1 of chemotherapy.[57] This is consistent with the individual phase 3 RCTs of US-available pegfilgrastim biosimilars that demonstrated bioequivalence to the pegfilgrastim originator based on duration of SN in chemotherapy cycle 1 among breast cancer patients.[186,187,196] With respect to overall safety, the safety profile of pegfilgrastim biosimilars seems similar to pegfilgrastim. Pegfilgrastim-jmdb exhibited a similar safety profile to pegfilgrastim at an equivalent dose (6 mg single-dose per chemotherapy cycle subQ) based on the incidence of treatment-emergent AEs (90% vs 87%) and types of AEs, such as bone pain (40% vs 36%, respectively).[186] Similarly, at equivalent doses (6 mg subQ), pegfilgrastim-bmez exhibited a similar safety profile to originator pegfilgrastim with respect to total treatment-emergent AEs, incidence of bone or musculoskeletal-related pain, and incidence of serious AEs. [187,188] **No neutralizing antibodies developed during these US-available biosimilar studies**.[186-188]

Filgrastim versus tbo-filgrastim

Primary Prophylaxis of CIN

Three phase 3 RCTs compared filgrastim to tbo-filgrastim during cycle 1 of chemotherapy (2 switch trials by **Engert et al[64] and Gatzmeir et al[65], 2009**) or across all cycles (**Del Giglio et al 2008[63]**), both at a dose of 5 mcg/kg/day subQ until ANC[65] recovery or a minimum of 5 days or maximum of 14 days. Included patients were adults with a solid tumor malignancy (breast cancer[63] or [non]small cell lung cancer[65]) or non-Hodgkin's lymphoma[64] (NHL) receiving myelosuppressive chemotherapy with cycle lengths of 3-4

weeks. Each trial showed a similar mean duration of severe neutropenia (ie, grade 4 neutropenia with ANC <0.5 x 10^9/L) between tbo-filgrastim and filgrastim groups during cycle 1.[63-65] **In the only trial powered to evaluate this primary efficacy outcome, statistical equivalence with respect to the duration of severe neutropenia was established** (1.1 vs 1.1 days, 95%CI –0.261 to 0.316 for the difference which was within ± 1 day for equivalency).[63] In each trial, tbo-filgrastim- and filgrastim-treated patients exhibited relatively similar mean ANC nadirs,[63-65] and time to ANC recovery[63,64] (except for possibly in the trial among lung cancer patients where the time was 6.3 days in the tbo-filgrastim arm vs 4.5 days with filgrastim).[65] Numerically, the incidence of FN (which was an exploratory analyses in 2 trials[64,65] and a secondary outcome in the 3rd trial[63]) in cycle 1 was slightly heterogeneous between treatment arms. Among breast cancer patients, numerically and statistically, a similar incidence of FN (20.7% vs 22.1%) was observed for tbo-filgrastim and filgrastim, respectively.[63] Yet among NHL and lung cancer patients, inconsistent, possible numeric differences (when not powered to assess statistical differences) in the incidence of FN for tbo-filgrastim vs filgrastim was observed: 15% vs 8.8% among lung cancer patients,[65] and 11.1% vs 20.7% among NHL patients.[64] Ultimately, an MA by **Engert et al 2009** pooled the 3 RCTs, confirming that filgrastim and tbo-filgrastim are similarly effective at preventing febrile neutropenia during cycle 1 of chemotherapy regardless of the degree of myelotoxic potential of the chemotherapy regimen.[61]

Overall, the safety profile was similar between treatment arms, with bone pain, arthralgia, fever, fatigue, headache, anemia, and diarrhea being among the most common AE.[63-65] **In the trial among breast cancer patients, the overall incidence of AE was significantly higher in the filgrastim group compared to the tbo-filgrastim group (39.7% vs 25.7%, P=0.0149**)[63]; this comparison was not reported for the other trials.

Mobilization of Peripheral Blood Stem Cells

One phase 2, open-label randomized trial by **Bhamidipati et al 2017** compared subcutaneous tbo-filgrastim to filgrastim (both 10 mcg/kg/day for 5 days given with co-mobilizer plerixafor on day 4) for mobilization of CD34+ cells before autologous HCT.[62] Included patients were adults with multiple myeloma (MM) or NHL, the majority of patients were diagnosed with MM (86%). **Tbo-filgrastim and filgrastim treatment resulted in a similar number of collected CD34+ cells on day 5**, 11.6 ± 6.7 cells/kg vs 10.0 ± 6.8 cells/kg (P=0.873), respectively. This exceeded the target goal of 5.0 x 10^6/kg for collection (for 96% of patients in each arm) and the majority (76-79%) of patients in each arm achieved this with 1 apheresis procedure. Investigators describe the study as a noninferiority trial, and list 12% as the noninferiority margin for the CD34+ cell collection primary outcome, but did not report the exact difference. Yet they did conclude that tbo-filgrastim was noninferior to filgrastim with respect to this outcome. Regarding secondary outcomes, tbo-filgrastim- and filgrastim-treated patients achieved similar numbers of peripheral blood CD34+ mobilized (measured in blood before apheresis) on day 5 and post-autologous HCT transplant-related outcomes of median time to neutrophil and platelet engraftment and hospitalization rate.[62]

Overall, the safety profile was similar between tbo-filgrastim and filgrastim. Both arms were similar with respect to the proportion of patients with a grade 3 or higher AE, serious AE, bone pain, anemia, thrombocytopenia, leukocytosis and increased ALP. The most common AE (not necessarily drug-related) were bone pain, thrombocytopenia, anemia, elevated ALP, and nausea/vomiting (which was not listed separately by treatment arm, but overall 21% of patients reported this event).[62]

Filgrastim versus sargramostim

We did not find any SRMA with RCTs of filgrastim versus sargramostim. A few SRs[197,198] and/or practice guidelines[124,192] included comparative trials and we reviewed these studies. **No randomized trials compared a G-CSF to sargramostim for an FDA-indicated or NCCN-recommended use that utilized FDA-approved dosing.** A couple randomized trials (Beveridge 1997, Weaver 2000) have compared filgrastim to sargramostim using non-standard doses for at least one of the products[66,68]; these studies are in the setting of prophylaxis of chemotherapy-induced neutropenia (CIN) (Beveridge 1997[66]) or for mobilization of peripheral blood stem cells (PBSCs) for autologous PBSCT (Weaver 2000)[68] in adults. One randomized trial used standard doses, but for an off-label use that is not routinely recommended in the 2015 ASCO guideline,[21] treatment of *afebrile* CIN (Beveridge 1998).[67] Despite the fact that most of the studied doses or uses may not be generalizable to practice, we will discuss the results of these studies below in light of the paucity of data comparing these medications. In addition, conclusions about the comparability of G-CSFs vs GM-CSFs from various clinical practice guidelines/position papers are incorporated.

A randomized trial suggests that **non-standard doses of filgrastim and sargramostim (filgrastim 7 mg/kg/day vs sargramostim 193 mg/m^2/day subQ) as prophylaxis of CIN in adults may be similarly tolerable, with minor differences in mild fever (favoring filgrastim) or mild bone pain (favoring sargramostim)**.[66] A second trial compared sargramostim (250 mcg/m^2/day subQ) to filgrastim (5 mcg/kg/day subQ) for treatment of afebrile CIN (ANC < 500/µL) in adult patients with a malignancy, finding that filgrastim-treated patients reached the target ANC (1500/µL) by an average of 1 day faster than sargramostim-treated patients. Overall it was concluded that sargramostim and filgrastim have similar efficacy and tolerability for treatment of afebrile neutropenia in ambulatory cancer patients as the average of 1 day difference ANC recovery was not considered to be clinically significant by authors.[67] A third RCT of filgrastim (6 mcg/kg/day subQ) versus sargramostim (250 mcg/m^2/day subQ), both after chemo-mobilization, among adult patients with a breast, lymphoma or multiple myeloma malignancy who would receive an autologous peripheral blood stem cell (PBSC) transplant for intensive chemotherapy support.[67] Filgrastim-mobilization resulted in a significantly higher median number of progenitor (CD34+) cells and required a fewer number of apheresis procedures and shorter CSF treatment duration to reach that number of CD34+ cells than sargramostim; however, this difference may depend on the chemo-mobilization regimen as the amount of mobilized cells was significantly different in one subgroup but not the other. Transplant-related outcomes (ie, incidence of hospitalizations, number of red blood cell transfusions, incidence of fever) favored filgrastim over sargramostim.[68]

Primary Prophylaxis (primarily) of CIN

Evidence-based guidelines or statements from the European Organization for Research and Treatment of Cancer (EORTC) [2010] and Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO) [2014] suggest that G-CSF and GM-CSF are *probably* comparable in efficacy for reducing the incidence and duration of neutropenia after myelosuppressive chemotherapy.[166] Although, the guideline from AGIHO/DGHO notes the lack of formal comparative evidence,[166] and cited evidence of comparability by the EORTC is limited due to it being either for a non-sargramostim GM-CSF or based on indirect comparisons of the outcomes of individual G-CSF or GM-CSF studies.[166] Similarly, the ASCO 2006 and 2015 guidelines on the use of CSFs chose not to make statement about the comparability of G-CSFs to GM-CSFs (for any indication) due to lack of or only limited

comparative data.[21,124] The NCCN does not recommend sargramostim for prophylaxis of FN unlike G-CSFs.[20] An SR by **Dubois et al (2004**) concluded there was a lack of evidence to compare G-CSFs to GM-CSF for prevention of chemotherapy-induced complications. They also suggest GM-CSF may not be effective as prophylaxis after myelosuppressive chemotherapy since 3 placebo-controlled trials demonstrated a similar incidence of febrile neutropenia and fever between GM-CSF and placebo.[198]

Beveridge et al 1997 performed randomized double-blind trial comparing filgrastim 7 mg/kg/day (n=62) to sargramostim 193 mg/m^2/day[††††] (n=75), both given subcutaneously by a trained patient, *for either prophylaxi*s (82% of cases) starting 1-2 days after myelosuppressive chemotherapy *or as treatment* for an absolute neutrophil count (ANC) <500/µL (18% of cases) in adults with any malignancy requiring chemotherapy.[67] The primary purpose of the study was to evaluate the relative *tolerability* of these regimens. Overall, both regimens exhibited similar tolerability. Most AE were of mild to moderate severity, and were similar between filgrastim and sargramostim arms except for a significantly higher rate of mild fever in the sargramostim group (48% vs 26%*, P=0.01*) and numerically more mild bone pain in the filgrastim arm (4% vs 9%), although the overall rate of bone pain was numerically similar (14% vs 12%).[66]

Treatment of Chemotherapy-induced Neutropenia in Afebrile Patients

Based on high-quality evidence, the ASCO does not recommend *routine* use of CSFs in afebrile adults with solid tumors/lymphoma who received chemotherapy and become neutropenic.[21]

Beveridge et al 1998 conducted a randomized, double-blind multi-center trial comparing sargramostim 250 mcg/m^2/day (n=79) to filgrastim 5 mcg/kg/day (n=102), both patient-administered subcutaneously, for a mean length of 5.7 days for sargramostim versus 4.6 days for filgrastim (P=0.001 for duration comparison) for treatment of *afebrile* chemotherapy-induced neutropenia (ANC < 500/µL) in adult patients with a malignancy.[67] Filgrastim-treated patients reached the target ANC for CSF discontinuation (1500/µL) by an average of about 1 day faster than sargramostim-treated patients (4.6 ± 0.14 vs 5.7 ± 0.23 days, P = 0.0001). The secondary outcome of requiring hospitalization was similar between arms, and both treatments exhibited similar tolerability. Overall, it was concluded that sargramostim and filgrastim have similar efficacy and tolerability for treatment of afebrile neutropenia in ambulatory cancer patients as the average of 1 day difference ANC recovery was not considered *clinically* significant by authors.[67]

Mobilization of Peripheral Blood Stem Cells

The ASTCT guideline (2014) for mobilization of PBSCs does not recommend GM-CSF monotherapy for mobilization for *allogeneic transplants* due to greater efficacy of G-CSF to mobilize CD34+ cells.[31] Although, most of the cited studies by ASTCT were limited owing to lack of randomization or did not specifically compare sargramostim to filgrastim (it is possible other GM-CSFs and/or G-CSFs were used). Similarly, NCCN (2021) only lists G-CSF as an option for allogeneic transplants, and *for autologous transplants,* GM-CSF is an option only when used in combination with chemotherapy unlike G-CSF.[30]

In the setting of autologous transplant, **Weaver et al 2000** conducted a randomized, open-label, multicenter trial comparing filgrastim 6 mcg/kg/day (n=51) to sargramostim 250 mcg/m^2/day (n=52), both administered subcutaneously starting the day after myelosuppressive chemotherapy given for

[††††] We wonder if the authors meant micrograms instead of milligrams. The recommended dose of filgrastim for prophylaxis is 5 mcg/kg/day and sagramostim is usually given as 250 mcg/m^2/day.

mobilization, and continued until collection of PBSCs among adults with a breast, lymphoma, or multiple myeloma malignancy who would receive an autologous PBSC transplant for intensive chemotherapy support.[68] **In the overall trial population, filgrastim-treated patients mobilized a significantly higher median number of progenitor (CD34+) cells and required a fewer number of apheresis procedures and shorter CSF treatment duration to reach that number of CD34+ cells than sargramostim-treated patients.** However, sargramostim and filgrastim were similarly effective for mobilization in one chemo-mobilization regimen but not the other. Transplant-related outcomes (ie, incidence of hospitalizations, number of red blood cell transfusions, incidence of fever) favored filgrastim over sargramostim. Comparative drug toxicity was not addressed.[68]

Safety

Common Adverse Events (AEs) Reported in Clinical Trials

Table 16 provides an overview of the most common side effects reported in clinical trials of these products, as included in the prescribing information (ie, package insert), with variation dependent on the studied population. Among filgrastim and filgrastim biosimilars, common AEs reported in 2 or more clinical trial populations include pain in bone, back, chest, or extremities; arthralgias, headache, rashes, thrombocytopenia, anemia, fatigue, dizziness, infections or fever and increased alkaline phosphatase.[3,10,11] For sargramostim, AEs were very variable by population; more than 1 population reported arthralgias, myalgia/bone pain, diarrhea, and low serum proteins/albumin. Examples of other reported AEs include infections or infection-related symptoms, cardiac AE, rashes, and metabolic laboratory abnormalities.[4] Both tbo-filgrastim and pegfilgrastim/pegfilgrastim biosimilars reported bone pain among adults with solid tumors or lymphoma receiving chemotherapy as a common AE.[13-18]

Prescribing information generally reports that the safety profile of each product is similar in special populations (pediatrics and older adults) relative to the general adult population when compared for indications for the respective population, though there may be insufficient data to fully distinguish any difference.[3,4,10,11,13-18]

According to a recent (2021) systemic review of G-CSF related adverse events, the most common AE of G-CSFs is short-term bone pain (also sometimes described as musculoskeletal pain) that is often mild to moderate in severity and does not usually cause an interruption in G-CSF treatment. Bone pain occurs at an estimated incidence of 10% to 30%.[20,199] **All formulations of G-CSFs, including short-acting and pegylated forms, are thought to have a similar safety profile**.[199,200] Options for managing bone pain include non-steroidal anti-inflammatory (NSAID) drugs or loratadine.[20]

The comparability of the safety profile of sargramostim to G-CSFs is not well established. The NCCN points out that sargramostim has primarily been studied in populations (eg, leukemias, transplant recipients) and using delivery routes (ie, intravenous) that differ from most G-CSF studies (primarily studied in non-myeloid malignancies).[20] This likely influences the reported safety profile. In 1 RCT comparing the safety profile of subcutaneous sargramostim to filgrastim at doses which might exceed those recommended for filgrastim and be below those recommended for sargramostim among adults receiving chemotherapy, a higher proportion of sargramostim-treated patients reported mild fever, but otherwise the incidence of AEs, including bone pain, was similar between study arms.[66]

Table 16. Overview of Common Adverse Events from Prescribing Information

Generic Name (brand)	Common Adverse Events in Clinical Trials by Reported Population
filgrastim[3] (Neupogen) **filgrastim-aafi**[10] (Nivestym) **Filgrastim-ayow**[12] (Releuko) **filgrastim-sndz**[11] (Zarxio)	Adults with solid tumor/lymphoma receiving MS chemo (incidence ≥ 5% and > PBO)[a]: • Thrombocytopenia, nausea, pyrexia, chest pain, pain, fatigue, back pain, arthralgia, bone pain (11% vs 6% PBO), extremity pain, dizziness, cough, dyspnea, rash, increased LDH and ALP Patients with AML (incidence ≥ 2% higher than PBO)[a]: • Epistaxis, back pain, pain in extremity, erythema, maculo-papular rash Patients undergoing BMT (incidence ≥ 5% higher than no filgrastim): • Rash, hypersensitivity Patients receiving intensive chemo + auto BMT (incidence ≥ 5% higher than no filgrastim): • Thrombocytopenia, anemia, hypertension, sepsis, bronchitis, insomnia Patients undergoing PBPC mobilization for auto transplant (incidence ≥ 5%): • Bone pain (30%), pyrexia, increased blood ALP, headache Patients with SCN (incidence ≥ 5% higher than no filgrastim): • Arthralgia, bone pain, back pain, muscle spasms, MSK pain, extremity pain, splenomegaly, anemia, URTI and UTI (total infections were fewer with treatment), epistaxis, chest pain, diarrhea, hypoesthesia, alopecia <u>Special populations</u> • Pediatric patients: generally similar safety profile to adults • Older adults: similar profile to younger adults among patients receiving MS chemo; insufficient data to comment on any differences in other populations
Tbo-filgrastim[13] (Granix)	Adults with solid tumor/lymphoma receiving MS chemo (TEAE incidence ≥ 1% and > PBO) • Bone pain (in cycle 1: 3.4% vs 1.4%) "Other adverse reactions known to occur…" with filgrastim products: • Myalgia, headache, vomiting, cutaneous vasculitis, thrombocytopenia <u>Special populations</u> • Pediatric patients (no info for age <1 month): similar safety profile to adults; most common AE: thrombocytopenia, pyrexia, extremity pain, headache, diarrhea • Older adults: similar safety profile to younger adults among patients receiving MS chemo

Table 16. Overview of Common Adverse Events from Prescribing Information

Generic Name (brand)	Common Adverse Events in Clinical Trials by Reported Population
Pegfilgrastim[14] (Neulasta) **Pegfilgrastim-jmdb**[15] (Fulphila) **Pegfilgrastim-apgf**[18] (Nyvepria) **Pegfilgrastim-cbqv**[16] (Udenyca) **Pegfilgrastim-bmez**[17] (Ziextenzo)	Adults with solid tumors or lymphoma receiving MS chemo (incidence ≥ 5% higher than PBO): • Bone pain (31% vs 26%), extremity pain Special populations • Pediatric patients: similar safety profile to adults • Older adults: similar safety profile to younger adults
Sargramostim[4] (Leukine)	Patients receiving auto PBPC or BM transplant (incidence ≥ 10% and ≥ 5% higher than PBO): • Asthenia, malaise, diarrhea, rash Patients receiving allo BMT (incidence ≥ 10% and ≥ 5% higher than PBO): • Abdominal pain, chills, chest pain, diarrhea, eye hemorrhage, hypomagnesemia, pharyngitis, GI hemorrhage, pruritis, bone pain (21% vs 5%), arthralgia, anxiety, grade 3/4 hyperglycemia, grade 3/4 low albumin Patients with AML receiving induction chemo (incidence ≥ 10% and ≥ 5% higher than PBO): • Fever without infection, weight loss, vomiting, skin reactions, metabolic laboratory abnormality, hypertension, cardiac AE, Graft failure [based on historical control study] (AE with statistically significant higher incidence versus control): • Weight gain, low serum proteins, prolonged PT time • Other AE reported in treated patients: headache, pericardiac effusion, arthralgia, myalgia Special populations • Pediatric patients: similar safety profile to adults among children (≥ 2 years) receiving an auto PBPC or BM transplant, allo BMT, or treatment of graft failure; safety not established for patients receiving treatment for neutrophil recovery after induction chemo for AML, or for mobilization of PBPC for autologous donors • Older adults: insufficient evidence to distinguish any differences

Abbreviations: AE, adverse event; Allo, allogeneic; ALP, alkaline phosphatase; AML, acute myeloid leukemia; auto, autologous; BM, bone marrow; BMT, bone marrow transplant; chemo, chemotherapy; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; LDH, lactate dehydrogenase; MS, myelosuppressive; MSK, musculoskeletal; PBPC, peripheral blood progenitor cell; PBO, placebo; PT, prothrombin; SCN, severe chronic neutropenia; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection

[a] Inferred as AEs considered unrelated to the underlying cancer or chemotherapy regimen

Contraindications, Warnings and Precautions

Refer to **Table 17** for an overview and **Appendix H** for more detail of labeled CSFs warnings and precautions. None of the products included in this review carry black box warnings. Each product is contraindicated in patients who have a history of allergy to the product, related products (ie, all G-CSFs), or components[3,4,10,11,13-17]; for sargramostim, this includes a history of allergy to yeast-derived products.[4]

Use of these products does introduce some risk. All of the G-CSFs (filgrastim and biosimilars, tbo-filgrastim, pegfilgrastim and biosimilars) carry similar warnings and precautions. There are a few exceptions that are product-specific, or may be omitted due to the lack of an indication for that use or other reasons unknown to the authors of this report. Filgrastim and similar products carry warnings about the time of administration relative to chemotherapy (do not administer 24 hours before or after chemotherapy) and to not use them with radiation[3,10,11]; pegfilgrastim and biosimilars are also not to be administered within 14 days before or 24 hours after chemotherapy.[14-17] More frequent neutropenia has been observed when G-CSFs are given too close to chemotherapy, which is suggested to occur from chemotherapy-induced destruction of a larger pool of neutrophil progenitors (increased by G-CSF).[201]

Filgrastim, its biosimilars, and tbo-filgrastim carry warnings for alveolar hemorrhage among healthy donors of peripheral blood progenitor cells, which is an off-label use.[3,10,11,13] A warning only among filgrastim and biosimilars is the risk for cutaneous vasculitis, which has been reported to occur in patients with severe chronic neutropenia, a population not indicated for use of the other G-CSF products.[3,10,11] Cases of cutaneous vasculitis have been reported with pegfilgrastim.[14] Filgrastim and biosimilars as well as pegfilgrastim and biosimilars carry two warnings not included on tbo-filgrastim labeling: risk for development of MDS and AML in certain patient populations, and development of thrombocytopenia.[3,10,11,14-17] Still, thrombocytopenia is a potential adverse effect of tbo-filgrastim.[13] The risk for developing MDS and AML is among the newest warnings added to pegfilgrastim- and filgrastim-based product labeling,[3,10,11,14-17] and according to the NCCN, this is expected to be a risk of all G-CSFs.[20] An MA of 25 RCTs showed an increased risk for these secondary malignancies with G-CSF use compared to no G-CSF among adults with solid tumors or lymphoma (RR 1.85, 95% CI 1.19 to 2.88), but the overall number of deaths avoided by G-CSF use exceeded the estimated occurrence of new malignancy.[104]

Sargramostim carries some similar warnings and precautions to the G-CSFs and a few other unique warnings. Shared warnings among all products, including sargramostim, are the risk for serious allergic reactions including anaphylaxis, development of capillary leak syndrome, excessive leukocytosis which necessitates monitoring, and that a possible growth effect on tumors, particularly among patients with myeloid tumors, cannot be excluded.[4,10,11,13-17] Similar to G-CSF products, sargramostim should not be given within 24 hours before or after chemotherapy or radiation.[4] Warnings unique to sargramostim include infusion-related reactions (eg, respiratory distress, hypotension), occurrence of supraventricular arrythmias, known cases of *neutralizing* anti-drug antibodies (ADA), and risk for serious adverse events in infants treated with the formulation containing benzyl alcohol.[4] The NCCN additionally warns to monitor patients with pre-existing renal or hepatic dysfunction before treatment.[20]

Unwanted immunogenicity is a primary safety concern of biosimilars, both during the initial development process and after regulatory approval (eg, owing to differences in a particular batch), which necessitates ongoing pharmacovigilance.[77] Sargramostim carries the warning for observed cases of *neutralizing* ADA[4]; though, development of ADA is a potential risk for all G-CSFs, including originator and biosimilar products.[3,10-18]

Table 17. Contraindications, Warnings and Precautions for Colony Stimulating Factors from Prescribing Information[a]

	filgrastim (Neupogen)[3] and biosimilars (Nivestym, Releuko, Zarxio)[10-12]	tbo-filgrastim (Granix)[13]	pegfilgrastim (Neulasta)[14] and biosimilars (Fulphila, Udenyca, Nyvepria, Ziextenzo)[10,15-18]	Sargramostim (Leukine)[4]
Contraindications				
	History of serious allergic reactions to G-CSFs (eg, filgrastim, pegfilgrastim)			History of serious allergic reactions to GM-CSFs or other product components, including products from yeast
Warnings and Precautions				
Serious allergic reactions or hypersensitivity reactions	**X**	**X**	**X**	**X**
CLS and/or effusions	**X**	**X**	**X**	**X**
Leukocytosis	**X**	**X**	**X**	**X**
Potential growth effect on malignant cells	**X**	**X**	**X**	**X**
Potentially fatal splenic rupture	**X**	**X**	**X**	
ARDS	**X**	**X**	**X**	
Severe sickle cell crises in people with SCD	**X**	**X**	**X**	
Glomerular nephritis	**X**	**X**	**X**	
Aortitis	**X**	**X**	**X**	
Bone nuclear imaging changes expected	**X**	**X**	**X**	
Thrombocytopenia	**X**		**X**	
Do not administer simultaneously with chemo or radiation	**X,** do not give within 24 hours before or after chemo; use with radiation has not been evaluated			**X**, do not give within 24 hours before or after chemo or radiation
Development of MDS or AML	**X,** for patients with lung or breast cancer, and severe congenital neutropenia		**X,** for patients with lung or breast cancer	

Table 17. Contraindications, Warnings and Precautions for Colony Stimulating Factors from Prescribing Information[a]

	filgrastim (Neupogen)[3] and biosimilars (Nivestym, Releuko, Zarxio)[10-12]	tbo-filgrastim (Granix)[13]	pegfilgrastim (Neulasta)[14] and biosimilars (Fulphila, Udenyca, Nyvepria, Ziextenzo)[10,15-18]	Sargramostim (Leukine)[4]
Alveolar hemorrhage in healthy donors during PBPC collection (not an approved indication)	**X**	**X**		
Cutaneous vasculitis	**X**, mostly in SCN patients			
Avoid use in patients with acrylic allergy			**X** (for OBI device only)	
Potential for device failure			**X** (for OBI device only)	
Infusion-related reactions				**X,** particularly with first dose in a cycle
Supraventricular arrythmias				**X,** use cautiously in patients with existing cardiac disorder
Immunogenicity with neutralizing anti-drug antibodies				**X,** use for minimum needed duration
Risk of serious adverse reactions, including fatalities, to benzyl alcohol				**X,** avoid giving benzyl alcohol containing products to neonates or low birth weight infants

Abbreviations: AE, adverse events; AML, acute myeloid leukemia; ARDS, acute respiratory distress syndrome; CLS, capillary leak syndrome; D/c, discontinue; G-CSFs, granulocyte colony-stimulating factors; GM-CSFs, granulocyte macrophage colony-stimulating factors (eg, sargramostim); MDS, myelodysplastic syndromes; OBI, on-body implant (refers to the Neulasta OnPro kit); PBPC, peripheral blood progenitor cell; SCN, severe chronic neutropenia;

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Appendix A: Detailed Indications and Dose Information from Package Inserts

Table 1. Colony Stimulating Factor Product Information from Package Inserts

Generic Name **Brand** and forms *Administration route* (Approval yr, manufacturer)	**FDA-approved Indications** *Limitations of use*	**Starting dose, duration, and monitoring**
Short-acting granulocyte colony-stimulating factors (G-CSF)		
Filgrastim[3] **Neupogen** • Vial for injection, single-dose: 300 mcg/mL; 480 mcg/1.6 mL • Prefilled syringe for injection, single-dose + needle safety guard: 300 mcg/0.5 mL; 480 mcg/0.8 mL *Vial: for IV or subQ use* *Syringe: for subQ use* • Latex allergy: do not use syringe (1991, Amgen)	1. Non-myeloid cancer patients receiving myelosuppressive chemo with high incidence of severe neutropenia/fever, *to decrease incidence of infection (febrile neutropenia)* 2. AML patients after induction or consolidation chemo, *to decrease the time to neutrophil recovery and length of fever*	1 & 2: **5 mcg/kg/day** subQ once daily, or IV infusion (15 to 30 minutes) once daily, or by continuous IV infusion. Start ≥ 24 hours after chemo. May increase dose by 5 mcg/kg/day per chemo cycle, as needed for ANC nadir severity. *Duration:* Daily for 2W or until ANC ≥ 10,000/mm^3 post nadir. *Monitoring:* CBC at BL and twice weekly during use. STOP use if ANC is ≥ 10,000/mm^3 post nadir.
	3. Non-myeloid cancer patients receiving a BMT after myeloablative chemo, *to decrease the duration of neutropenia/reduce neutropenic sequelae*	3: **10 mcg/kg/day** by ≤ 24 hour IV infusion. Start ≥ 24 hours after chemo and ≥ 24 hours after receipt of bone marrow. Adjust daily dose based on ANC recovery. *Monitoring:* CBC frequently. STOP if ANC >1,000/mm^3 for 6 consecutive days.
	4. For autologous progenitor cell collection, *to mobilize hematopoietic progenitor cells for leukapheresis*	4: **10 mcg/kg/day** subQ once daily. Start ≥ 4 days before 1st leukapheresis, and continue until leukapheresis is finished. *Monitoring:* Neutrophil count after 4 treatment days; STOP if WBC count reaches >100,000/mm^3.
	5. Patients with symptomatic chronic neutropenia[a], *for chronic use to decrease neutropenic sequelae.* Confirm diagnosis before use.	5: Congenital neutropenia: **6 mcg/kg** SUBQ twice daily; Idiopathic/cyclic neutropenia: **5 mcg/kg** subQ once daily. Adjust dose based on patient response. *Duration:* chronic *Monitoring:* CBC more frequently initially, then less frequent once patient is clinically stable.
	6. Patients who acutely received myelosuppressive radiation doses, *to increase survival*. Start after suspected/confirmed exposure > 2Gy.	6: **10 mcg/kg** subQ once daily. *Duration:* until ANC >1,000/mm^3 for 3 consecutive CBC checks, or until ANC ≥10,000/mm^3 post nadir.
Filgrastim-aafi[10] *Biosimilar to Neupogen* **Nivestym**	Same 1-5 indications as Neupogen (NOT for indication 6, treatment after myelosuppressive radiation).	Same dosing as Neupogen (for indications 1-5)

Table 1. Colony Stimulating Factor Product Information from Package Inserts

• Vial for injection, single-dose: 300 mcg/mL; 480 mcg/1.6 mL • Prefilled syringe for injection, single-dose + needle safety guard: 300 mcg/0.5 mL; 480 mcg/0.8 mL *Vial: for IV or subQ use* *Syringe: for subQ use* (2018, Pfizer Inc.)		Prefilled syringe should not be used for doses < 0.3mL (180 mcg) due to potential inaccuracy
Filgrastim-ayow[12] *Biosimilar to Neupogen* **Releuko** • Vial for injection, single-dose: 300 mcg/mL; 480 mcg/1.6 mL • Prefilled syringe for injection, single-dose + needle safety guard: 300 mcg/0.5 mL; 480 mcg/0.8 mL *Vial: for IV or subQ use* *Syringe: for subQ use* (2022, Kashiv/Amneal Biosciences)	Same 1-3 & 5 indications as Neupogen (NOT for indications 4, mobilization of autologous progenitor cells; or 6, treatment after myelosuppressive radiation).	Same dosing as Neupogen (for indications 1-3, 5) Prefilled syringe should not be used for doses < 0.3mL (180 mcg) due to potential inaccuracy
Filgrastim-sndz[11] *Biosimilar to Neupogen* **Zarxio** • Prefilled syringe for injection, single-dose + needle safety guard: 300 mcg/0.5 mL; 480 mcg/0.8 mL • Latex allergy: do not use syringe *Dilute syringe contents for IV administration, or use for subQ administration.* (2015, Sandoz Inc.)	Same 1-5 indications as Neupogen (NOT for indication 6, treatment after myelosuppressive radiation).	Same dosing as Neupogen (for indications 1-5) Prefilled syringe should not be used for doses < 0.3mL (180 mcg) due to potential inaccuracy

Table 1. Colony Stimulating Factor Product Information from Package Inserts

Tbo-filgrastim[13] **Granix** • Vial for injection, single-dose: 300 mcg/mL; 480 mcg/1.6 mL • Prefilled syringe for injection, single-dose ± needle safety guard: 300 mcg/0.5 mL; 480 mcg/0.8 mL *For subQ use* (2012, Teva Pharmaceuticals)	1. Non-myeloid cancer patients receiving myelosuppressive chemo with high incidence of severe neutropenia/fever, *to decrease duration of severe neutropenia* • Age: ≥ 1 month	1: **5 mcg/kg** subQ once daily. Start ≥ 24 hours after chemo. *Duration:* Continue daily until neutrophil recovery to normal range. *Monitoring:* CBC at BL and twice weekly during use.
Long-acting granulocyte colony-stimulating factors (G-CSF)		
Pegfilgrastim[14] **Neulasta** • Prefilled syringe for injection, single-dose + needle safety guard; for manual use: 6 mg/0.6 mL • Prefilled syringe for injection, single-dose; co-packaged with on-body injector (Neulasta Onpro Kit): 6 mg/0.6 mL • Latex allergy: do not use syringes *subQ use* (2002, Amgen)	1. Non-myeloid cancer patients receiving myelosuppressive chemo with high incidence of severe neutropenia/fever, *to decrease incidence of infection (febrile neutropenia)* 2. Patients who acutely received myelosuppressive radiation doses, *to increase survival*. Start after suspected/confirmed exposure > 2Gy. *Limitations of use:* • Not for blood progenitor cell mobilization for SCT *On-body injector* is not recommended for treatment of acute radiation syndrome, and its use has not been studied in children.	1. **6 mg** subQ once *per chemo cycle*. Do not administer between 14 days before to ≤ 24 hrs after chemo. *For weight < 45 kg*: use smaller, weight-based doses[b] . Direct administration of the prefilled syringe to these patients (requiring volumes <0.6 mL) is not recommended due to potential inaccuracy. 2. **Two 6 mg** doses, subQ one week apart. *For weight < 45 kg*: use smaller, weight-based doses[b] . Direct administration of the prefilled syringe to these patients (requiring volumes <0.6 mL) is NOT recommended due to potential inaccuracy. *Monitoring:* BL CBC
Pegfilgrastim-jmdb[15] *Biosimilar to Neulasta* **Fulphila** • Prefilled syringe for injection, single-dose + needle safety guard; for manual use: 6 mg/0.6 mL	1. Non-myeloid cancer patients receiving myelosuppressive chemo with high incidence of severe neutropenia/fever, *to decrease incidence of infection (febrile neutropenia)* *Limitations of use:*	1. **6 mg** subQ once *per chemo cycle*. Do not administer between 14 days before to ≤ 24 hrs after of chemo *For weight < 45 kg*: use smaller, weight-based doses[b] . Direct administration of the prefilled syringe to these patients (requiring volumes <0.6 mL) is NOT recommended due to potential inaccuracy.

Table 1. Colony Stimulating Factor Product Information from Package Inserts

SUBQ use (2018, Mylan Pharmaceuticals Inc.)	• Not for blood progenitor cell mobilization for SCT	
Pegfilgrastim-apgf[18] *Biosimilar to Neulasta* **Nyvepria** • Prefilled syringe for injection, single-dose + needle safety guard; for manual use: 6 mg/0.6 mL *SUBQ use* (2020, Pfizer Inc.)		
Pegfilgrastim-cbqv[16] *Biosimilar to Neulasta* **Udenyca** • Prefilled syringe for injection, single-dose + needle safety guard; for manual use: 6 mg/0.6 mL *SUBQ use* (2018, Coherus BioSciences)		
Pegfilgrastim-bmez[17] *Biosimilar to Neulasta* **Ziextenzo** • Prefilled syringe for injection, single-dose + needle safety guard; for manual use: 6 mg/0.6 mL • Latex allergy: do not use syringes *SUBQ use* (2019, Sandoz Inc.)		
Granulocyte macrophage colony-stimulating factor (GM-CSF)		
Sargramostim[4] **Leukine** • Lyophilized powder for injection, single-dose vial: 250 mcg	1. AML patients post induction chemo, *to hasten neutrophil recovery and reduce occurrence of infectious sequelae* • Age: ≥ 55 years	1. **250 mcg/m^2/day** IV infusion over 4 hrs, starting 4 days after completion of induction chem if there is hypoplastic bone marrow (<5% blasts). Do not administer within 24 hrs of chemo or radiotherapy. May administer after 2nd induction chemo. Adjust (50% reduction)

Table 1. Colony Stimulating Factor Product Information from Package Inserts

• Solution for injection, multi-dose vial: 500 mcg/mL • Solution contains 1.1% benzyl alcohol (avoid use for neonates/infants, during pregnancy) (1991, Sanofi-Aventis U.S. LLC)		or hold dose if grade 3 or 4 AE, of if ANC >20,000/mm^3 *Duration:* daily until ANC > 1500/mm^3 for 3 consecutive days or 42 days max. Discontinue treatment if lab results show leukemia growth. *Monitoring:* CBC with differential twice weekly
	2. For autologous progenitor cell collection, *to mobilize blood progenitor cells for leukapheresis* • Age: adults	2. **250 mcg/m^2/day** IV infusion over 24 hrs OR subQ once daily. Reduce dose (50%) if WBC >50,000/mm^3 *Duration*: daily during PBPC collection
	3. After autologous bone marrow/blood progenitor cell transplant for NHL, ALL or HL, *for faster myeloid reconstitution* • Age: ≥ 2 years	3. For PBPC transplant: **250 mcg/m^2 daily** IV infusion over 24 hrs, starting right after PBPC infusion. For BMT: **250 mcg/m^2 daily** IV infusion over 2 hrs, starting 2-4 hrs after bone marrow infusion and when ANC is <500/mm^3 *Duration:* daily until ANC >1500/mm^3 for 3 consecutive days. Do not give within 24 hrs or chemo/radiotherapy.
	4. After allogeneic BMT, *for faster myeloid reconstitution* • Age: ≥ 2 years	4. **250 mcg/m^2 daily** IV infusion over 2 hrs, starting 2-4 hrs after bone marrow infusion and when ANC is <500/mm^3. Do not give within 24 hrs or chemo/radiotherapy. Adjust (50% reduction) or hold dose if grade 3 or 4 AE; of if WBC >50,000/mm3 or ANC >20,000/mm^3 *Duration:* daily until ANC >1500/mm^3 for 3 consecutive days. STOP treatment if there is disease progression or blasts. *Monitoring:* CBC with differential twice weekly
	5. Treatment of delayed/failed neutrophil recovery after autologous or allogeneic BMT • Age: ≥ 2 years	5. **250 mcg/m^2 daily** IV infusion over 2 hrs. Adjust (50% reduction) or hold dose if grade 3 or 4 AE; of if WBC >50,000/mm3 or ANC >20,000/mm^3 *Duration:* 14 days. Can repeat again after 7 days off treatment if still no recovery. May administer a 3rd course at a higher dose (500 mcg/m^2/day) x 14 days if no recovery after 2 dose course. STOP treatment is disease progression or blasts. *Monitoring:* CBC with differential twice weekly

Table 1. Colony Stimulating Factor Product Information from Package Inserts

	6. Patients who acutely received myelosuppressive radiation doses, *to increase survival*. Start after suspected/confirmed exposure > 2Gy. • Age: birth to adults	6. **Weight-based dose** subQ once daily (wt >40 kg: 7 mcg/kg; wt 15 kg to 40 kg: 10 mcg/kg; wt <15 kg: 12 mcg/kg) *Duration:* until ANC >1,000/mm^3 for 3 CBC in a row or ANC >10,000/mm^3 post nadir *Monitoring:* CBC with differential then CBC about every 3rd day

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; BL, baseline; CBC, complete blood count; BMT, bone marrow transplant; chemo, chemotherapy; Gy, gray; HL, Hodgkin's lymphoma; IV, intravenous; max, maximum; mcg, micrograms; mL, milliliter; NHL, non-Hodgkin's lymphoma; PBPC, peripheral blood progenitor cell; SCT, stem cell transplant; SUBQ, subcutaneous; W, week; WBC, white blood cell; weight, wt; yr, year

[a] Severe chronic neutropenia patients listed: congenital neutropenia, cyclic neutropenia, idiopathic neutropenia

[b] Specific doses are provided per body weight range. Consult prescribing information.

Appendix B: Literature Searches

Systematic Review Search in Ovid-Medline

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily** 1946 to January 24, 2022

Search Strategy:

#	Searches	Results
1	(filgrastim or pegfilgrastim or peg-filgrastim or sargramostim or neupogen or granix or nivestym or zarxio or neulasta or fulphila or nyvepria or udenyca or ziextenzo or leukine).ti,ab,kw,kf.	2830
2	*granulocyte colony-stimulating factor/ or *filgrastim/ or *granulocyte-macrophage colony-stimulating factor/	15597
3	*Colony-Stimulating Factors/	3097
4	("Granulocyte colony stimulating factor*" or "granulocyte macrophage colony stimulating factor*").ti,ab,kw,kf.	28869
5	1 or 2 or 3 or 4	36219
6	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	436218
7	(MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt.	406788
8	6 or 7	509860
9	5 and 8	443

Systematic Review Search in Embase

Search date: February 3, 2022. Sources searched: Embase, Medline, Preprints

No. Query	Results
#13 #12 AND (**2011**:py OR **2012**:py OR **2013**:py OR **2014**:py OR **2015**:py OR **2016**:py OR **2017**:py OR **2018**:py OR **2019**:py OR **2020**:py OR **2021**:py OR **2022**:py)	**311**
#12 #9 AND #11	**503**
#11	**461,865**

(**cochrane***:jt OR **'systematic review*'**:jt OR **'meta analysis'**/exp OR **'systematic review'**/exp OR ((**systematic*** NEAR/3 **review***):ti,ab,kw) OR ((**systematic*** NEAR/2 **search***):ti,ab,kw) OR **'meta analys*'**:ti,ab,kw OR **metaanalys***:ti,ab,kw OR ((**overview** NEAR/4 (**review** OR **reviews**)):ti)) NOT (**'conference abstract'**/it OR **'conference review'**/it) AND [english]/lim

42,065

#10
#4 OR **#7** OR **#8**

44,593

#9
#6 OR **#7** OR **#8**

34,870

#8
'granulocyte colony stimulating factor*':ti,ab,kw OR **'granulocyte macrophage colony stimulating factor*'**:ti,ab,kw

5,632

#7
filgrastim:ti,ab,kw OR **pegfilgrastim**:ti,ab,kw OR **'peg filgrastim'**:ti,ab,kw OR **sargramostim**:ti,ab,kw OR **neupogen**:ti,ab,kw OR **granix**:ti,ab,kw OR **nivestym**:ti,ab,kw OR **zarxio**:ti,ab,kw OR **neulasta**:ti,ab,kw OR **fulphila**:ti,ab,kw OR **nyvepria**:ti,ab,kw OR **udenyca**:ti,ab,kw OR **ziextenzo**:ti,ab,kw OR **leukine**:ti,ab,kw

14,186

#6
#4 OR **#5**

3,406

#5
'colony stimulating factor'/mj

10,873

#4
#1 OR **#2** OR **#3**

4,551

#3
'pegfilgrastim'/exp OR **'filgrastim'**/exp

5,022

#2
'recombinant granulocyte colony stimulating factor'/mj

1,738

#1
'recombinant granulocyte macrophage colony stimulating factor'/mj

Systematic Review Search in Epistemonikos

(title:((title:((colony stimulating factor*) OR filgrastim OR pegfilgrastim OR peg-filgrastim OR sargramostim) OR abstract:((colony stimulating factor*) OR filgrastim OR pegfilgrastim OR peg-filgrastim OR sargramostim))) OR abstract:((title:((colony stimulating factor*) OR filgrastim OR pegfilgrastim OR peg-filgrastim OR sargramostim) OR abstract:((colony stimulating factor*) OR filgrastim OR pegfilgrastim OR peg-filgrastim OR sargramostim))))

+ Filtered results using the Epistemonikos publication type filter “Systematic Review”

Total = 106. Search date: February 3, 2022.

Randomized Controlled Trial Search in Ovid

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily** 1946 to February 11, 2022
Search Strategy:

#	Searches	Results
1	(filgrastim or pegfilgrastim or peg-filgrastim or sargramostim or neupogen or granix or XM02 or XM-02 or biograstim or ratiograstim or tevagrastim or neulasta or leukine).ti,ab,kw,kf.	2841
2	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1312150
3	*Filgrastim/	365
4	1 or 3	2873
5	2 and 4	806
6	limit 5 to yr="2014 -Current"	217

Randomized Controlled Trial Search in Embase

Search date: February 14, 2022.

No.	Query	Results
#10	#8 NOT #4 AND [2014-2022]/py	279
#9	#8 NOT #4	812
#8	#5 AND #7	832
#7	#1 OR #6	5,810
#6		1,160

'pegfilgrastim'/mj OR **'filgrastim'**/mj

2,341,006

#5

(**'crossover procedure'**:de OR **'double-blind procedure'**:de OR **'randomized controlled trial'**:de OR **'single-blind procedure'**:de OR **random***:de,ab,ti OR **factorial***:de,ab,ti OR **crossover***:de,ab,ti OR ((**cross** NEXT/1 **over***):de,ab,ti) OR **placebo***:de,ab,ti OR ((**doubl*** NEAR/1 **blind***):de,ab,ti) OR ((**singl*** NEAR/1 **blind***):de,ab,ti) OR **assign***:de,ab,ti OR **allocat***:de,ab,ti OR **volunteer***:de,ab,ti) NOT (**'conference abstract'**/it OR **'conference review'**/it)

7,971,330

#4

#2 OR **#3**

7,432,632

#3

(**'animal'**/exp OR **'invertebrate'**/exp OR **'animal experiment'**/exp OR **'animal model'**/exp OR **'animal tissue'**/exp OR **'animal cell'**/exp OR **'nonhuman'**/de) NOT ((**'animal'**/exp OR **'invertebrate'**/exp OR **'animal experiment'**/exp OR **'animal model'**/exp OR **'animal tissue'**/exp OR **'animal cell'**/exp OR **'nonhuman'**/de) AND (**'human'**/exp OR **'human cell'**/de))

2,992,063

#2

animal*:ti OR **beaver***:ti OR **beef**:ti OR **bovine**:ti OR **breeding**:ti OR **canine**:ti OR **castoris**:ti OR **cat**:ti OR **cattle**:ti OR **cats**:ti OR **chicken***:ti OR **cow**:ti OR **dog**:ti OR **dogs**:ti OR **equine**:ti OR **foal**:ti OR **foals**:ti OR **fish**:ti OR **insect***:ti OR **livestock**:ti OR **mice**:ti OR **mouse**:ti OR **murine**:ti OR **plant**:ti OR **plants**:ti OR **pork**:ti OR **porcine**:ti OR **protozoa***:ti OR **purebred**:ti OR **rabbit***:ti OR **rat**:ti OR **rats**:ti OR **rodent***:ti OR **sheep**:ti OR **thoroughbred**:ti OR **veterinar***:ti,ab,de

5,648

#1

filgrastim:ti,ab,kw OR **pegfilgrastim**:ti,ab,kw OR **'peg filgrastim'**:ti,ab,kw OR **sargramostim**:ti,ab,kw OR **neupogen**:ti,ab,kw OR **granix**:ti,ab,kw OR **xm02**:ti,ab,kw OR **'xm 02'**:ti,ab,kw OR **biograstim**:ti,ab,kw OR **ratiograstim**:ti,ab,kw OR **tevagrastim**:ti,ab,kw OR **neulasta**:ti,ab,kw OR **leukine**:ti,ab,kw

Targeted Search for New Product (filgrastim-ayow)

Search in Ovid-Medline (search date: March 16, 2022): (Releuko or filgrastim-ayow).ti,ab,kw,kf.

- Returned no results

Search in Embase (search date: March 16, 2022): releuko:ti,ab,kw OR 'filgrastim ayow':ti,ab,kw

- Returned no results

Appendix C: Other Guidelines Screened for CSF Recommendations

Table 1. Excluded Screened Clinical Practice Guidelines

Notes on Guideline-Screening Process
• We screened NCCN guidelines for recommendations for use of G-CSF based on searching for key words (ie, filgrastim, pegfilgrastim, sargramostim, G-CSF, GM-CSF, colony stimulating factor, growth factor) in guidelines for supportive care and specific populations. For NCCN disease-specific guidelines, this key word approach was used to search among guidelines addressing myeloid disorders, leukemias, lymphomas, pediatric disorders (according to guideline title), and selected other disorders • The NCCN drug and biologics compendium was additionally searched to identify guidelines with recommendations for use of filgrastim or biosimilar, pegfilgrastim or biosimilar and sargramostim. • Non-NCCN guidelines were identified based on lists on the websites of US organizations related to on-label uses of G-CSFs or GM-CSFs (eg, oncology, stem cell transplant). Selected additional guidelines were searched based on off-label uses with the highest recommendations for use in Micromedex (eg, related to sepsis).
NCCN guidelines screened that lacked a specific recommendation
(Note that use of G-CSFs or GM-CSFs in some of these populations is addressed by other guidelines) • Breast cancer 2.2022 • Anal carcinoma 1.2022 • Hodgkin lymphoma 1.2022 • Multiple myeloma 4.2022 • Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes 4.2021 • Occult primary (cancer of unknown primary) 1.2022 • Pediatric Hodgkin lymphoma 3.2021: only mentions “growth factors” used in one particular regimen in the details section. • Primary Cutaneous Lymphomas 2.2021: only mentions GM-CSF in the details of one particular regimen from a clinical trial • Systemic Light Chain Amyloidosis 1.2022 • Peripheral T-cell lymphomas 1.2022: only mentions G-CSF used in a particular regimen in a clinical trial • Lymphoplasmacytic lymphoma 2.022 • Bone cancer 2.2022: refers readers to the NCCN hematopoietic GFs guideline • Cancer in people with HIV 2.2021 • Older adult oncology 1.2021: no formal recommendations, refers to the NCCN hematopoietic GFs guideline. “Prophylactic colony-stimulating factors are needed when dose intensity is required for response or cure”; “The risk of myelosuppression is decreased by 50% when using growth factors.”[202] • Adolescent and young adult oncology 2.022: refers to the NCCN hematopoietic GFs guideline • Palliative care 2.2021
Non-NCCN guidelines screened that lacked a specific recommendation
• 2018 IDSA/ASCO –treatment of neutropenic fever in cancer patients; They refer readers to the 2015 ASCO guideline on use of WBC growth factors. • Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children” (2020) • WHO recommendations on Newborn Health (2017) • AAP (2018): Management of Neonates Born at ≤34 6/7 weeks gestation with suspected or proven early-onset bacterial sepsis

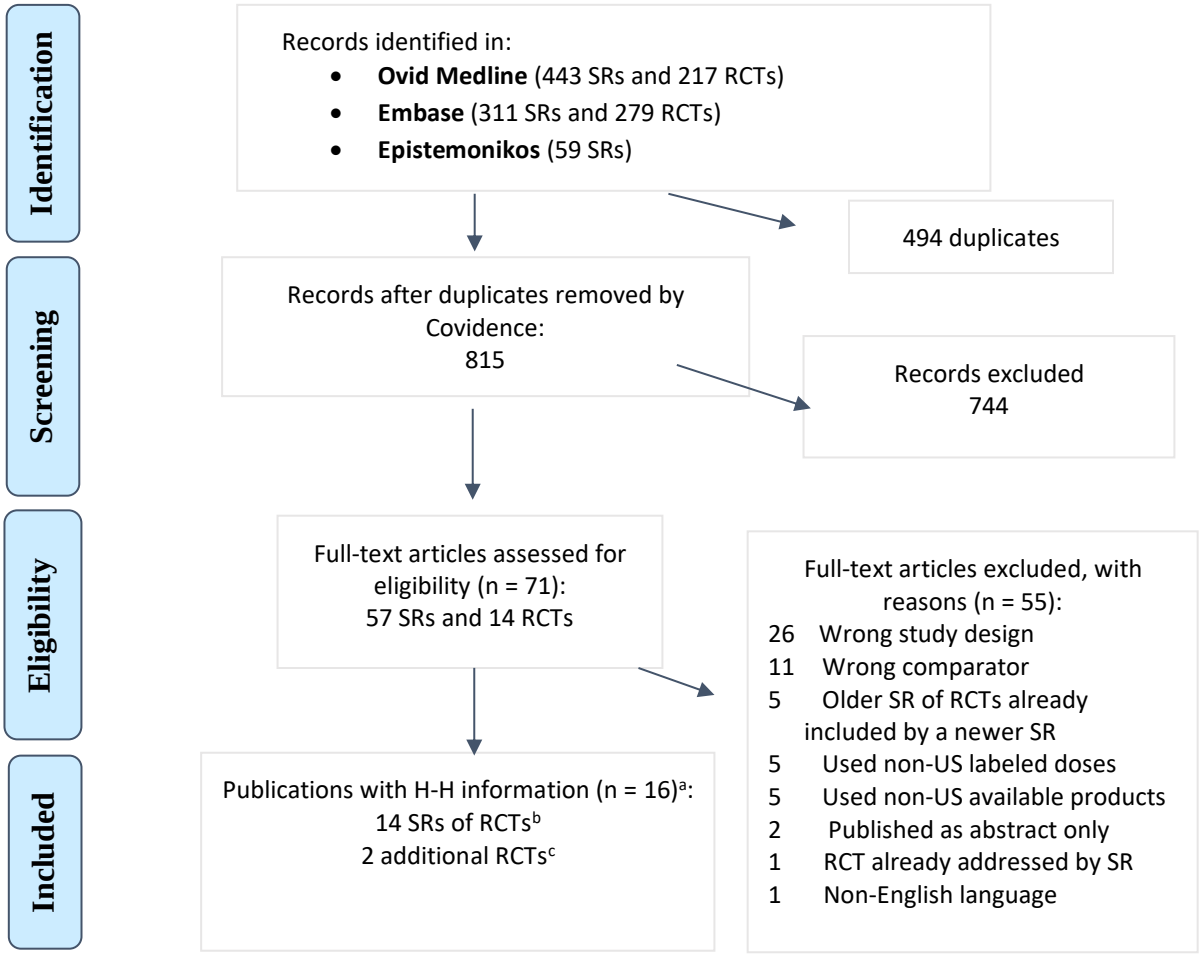
Table 1. Excluded Screened Clinical Practice Guidelines

- AAP (2018): Management of Neonates Born at ≥35 0/7 weeks gestation with suspected or proven early-onset bacterial sepsis
- NICE Sepsis Quality Standard (updated 2020)
- ASH: Guidelines for treating newly diagnosed acute myeloid leukemia in older adults (2020)
- ASCO multiple myeloma guideline (2019): only mentions "Although some deleterious effects from alkylator and lenalidomide exposure can be overcome by either combination of growth factor and chemotherapy or growth factor and chemotherapy or growth factor and CXCR4 antagonist (plerixafor), prolonged exposure (>cycles) to these agents should be avoided prior to stem-cell mobilization."[203]
- The International Pediatric Fever and Neutropenia Guideline (2017)
- ASCO Clinical Practice Guideline Update: Use of Chemotherapy and Radiation Therapy Protectants (2008): In the context of use of amifostine for chemo-induced neutropenia, mentions "…the clinician may reasonably consider alternative strategies such as the use of myeloid growth factor support or chemotherapy dose reduction to ameliorate neutropenia"[204]
- ASTCT: Hematopoietic Cell Transplantation for the Treatment of Adult Acute Lymphoblastic Leukemia (2019)
- ASTCT: Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the Society for Blood and Marrow Transplantation (2015)
- ASTCT: Role of Cytotoxic Therapy with Hematopoietic Cell Transplantation in the Treatment of Hodgkin Lymphoma: Guidelines from the American Society for Blood and Marrow Transplantation (2015)
- ASTCT: First- and Second-Line Systemic Treatment of Acute Graft-versus-Host Disease (2012)

Abbreviations: AAP, American Academy of Pediatrics; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; ASTCT, American Society for Transplantation and Cellular Therapy; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; WHO, World Health Organization;

Appendix D: Screening of Studies

Figure 1. PRISMA Flow Chart for Publication Screening



Abbreviations: H-H, head to head; n, number; RCT, randomized controlled trial; SR, systematic review; US, United States

[a] A total of 18 SRs or RCTs are included if you count 2 additional studies identified from review text (see below)
[b] Two SRs addressing use of sagramostim are included because they identified 1 RCT each. However, we extracted details from the RCTs and these studies are summarized separately from the evidence tables. Additionally, other trials of sargramostim (2 additional) which were identified from non-SRs are additionally included.
[c] RCT evidence table or summary text includes 7 trials included among SRs or identifed from reviews (sargramostim); only 4 RCTs not addressed in an SR or review are separately included

Appendix E: Level of Evidence from Select Guidelines

Table 1. Level of Evidence Definitions for Select Included Guidelines/Organizations

National Comprehensive Cancer Network (NCCN) Guidelines

- The NCCN is a non-profit organization represented by 31 cancer centers across the US
- Guideline panelists consist of representatives from one of the 31 institutions, and may also include others (eg, patients, primary care providers)
- These guidelines are updated frequently (minimum of annually) as new drugs are approved or new studies are published[205]

Category of Evidence	Definition[205]
1	"Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate" • Requires majority vote of ≥ 85% of the panel
2A	"Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate" • Requires majority vote of ≥ 85% of the panel
2B	"Based upon lower-level evidence, there is NCCN consensus that intervention is appropriate" • Requires majority vote of ≥ 50% (and ≤ 85%) of the panel
3	"Based on any level of evidence, there is major NCCN disagreement that the intervention is appropriate" • Requires panel agreement of at least 25%

American Society of Clinical Oncology (ASCO) Guidelines[21,a]

- ASCO categorizes the recommendations in multiple ways:
  - (1) Type of recommendation: evidence-based, formal consensus, informal consensus, or no recommendations
  - (2) Strength of recommendation: strong, moderate, or weak
  - (3) Strength of evidence: high, intermediate, low, or insufficient

  They also considered the risk for bias (high vs intermediate vs low), and this was apparently incorporated into recommendations in other categories.

Recommendation type	Definition
Evidence-based	Made based on sufficient informative evidence
Formal Consensus	Insufficient evidence; expert panel achieved formal consensus
Informal Consensus	Insufficient evidence; expert panel elected not to go through formal consensus
No Recommendation	Insufficient evidence or confidence for a recommendation, or lack of expert panel agreement
Strength of Recommendation	**Definition** (reflects degree of confidence based on: evidence of benefits>harms with consistency, any bias concerns, and degree of agreement by the expert panelists)
Strong	High confidence
Moderate	Moderate confidence
Weak	Some confidence

Table 1. Level of Evidence Definitions for Select Included Guidelines/Organizations

Strength of Evidence	Definition (reflects degree of confidence in light of likelihood of observed evidence being reflective of the true measured effect [magnitude and direction], and whether additional evidence would change the observed effect)
High	High confidence – likely the true effect and additional studies will not change it
Intermediate	Moderate confidence – likely the true effect; additional studies could change the effect size but not the direction of effect
Low	Low confidence – about truth of the effect and how any additional studies might change it.
Insufficient	Gathered evidence is insufficient for any confidence about the true effect.
American Society for Blood and Marrow Transplantation (ASBMT)[b,c]	
Level of Evidence	*All of the following studies must be considered high-quality or well-conducted*
1++	SR or MA of RCTs, or RCTs, judged to have very low bias risk
1+	SR or MA of RCTs, or RCTs, judged to have very low bias risk
2++	SR of observational studies (cohort, case-control) with a high likelihood for a causal relationship and very low bias risk
2+	Observational studies (cohort, case-control) with a moderate likelihood for a causal relationship and low bias risk
Recommendation Grade	
A	"At least 1 meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results"[31]
B	**"**A body of evidence including studies rated as 2++, and directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rates as 1++ or 1+"[31]
C	**"**A body of evidence including studies rates as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++"[31]
D	**"**Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+"[31]

Abbreviations: MA, meta-analysis; RCT, randomized controlled trial; SR, systematic review; Vs, versus

[a] This is from the methodology for the ASCO 2015 guideline on recommended uses for white blood cell growth factors which may not be consistent with all ASCO guidelines
[b] This organization is now called the American Society for Transplantation and Cellular Therapy. Information presented is based on the 2014 guideline
[c] From the 2014 Peripheral Blood Progenitor Cell Mobilization guideline

Appendix F: Excluded Full-Text Studies

The most common reasons for exclusion were the wrong study design (n = 26), followed by wrong comparator (n = 11). Examples of 'wrong study design' are non-SR review articles based on the fact that they did not report a literature search of at least 2 databases, or SRs of non-RCTs (eg, observational studies). Most studies excluded for 'wrong comparator' only included placebo comparators.

Abstract only

1. Sun D, Gharaibeh M, Altyar A, MacDonald K, Martin J, Abraham I. Economic Evaluation of Primary Prophylaxis Using Filgrastim Versus Pegfilgrastim in Patients With Solid Tumor Cancer: A Systematic Literature Review. Value Health. 2014;17(7):A736.
2. Wang L, Baser O, Kutikova L, Page JH, Barron RL. The impact of primary prophylaxis with granulocyte colony-stimulating factors on febrile neutropenia during chemotherapy: A systematic review and meta-analysis of randomized controlled trials. Blood. 2014;124(21).

Addressed by included SR

3. Kuan JW, Su AT, Wong SP, et al. A randomized double blind control trial comparing filgrastim and pegfilgrastim in cyclophosphamide peripheral blood hematopoietic stem cell mobilization. Transfus Apher Sci. 2015;53(2):196-204.

Non-English language

4. Yang S, He X, Liu P, et al. Efficacy analysis of pegylated filgrastim as prophylaxis for chemotherapy-induced neutropenia. Chinese Journal of Clinical Oncology. 2015;42(12):626-631.

Older SR of already included RCTs

5. Wang L, Baser O, Kutikova L, Page JH, Barron R. The impact of primary prophylaxis with granulocyte colony-stimulating factors on febrile neutropenia during chemotherapy: a systematic review and meta-analysis of randomized controlled trials. Support Care Cancer. 2015;23(11):3131-3140.
6. Pinto L, Liu Z, Doan Q, Bernal M, Dubois R, Lyman G. Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. Curr Med Res Opin. 2007;23(9):2283-2295.
7. Pfeil AM, Allcott K, Pettengell R, von Minckwitz G, Schwenkglenks M, Szabo Z. Efficacy, effectiveness and safety of long-acting granulocyte colony-stimulating factors for prophylaxis of chemotherapy-induced neutropenia in patients with cancer: a systematic review. Support Care Cancer. 2015;23(2):525-545.
8. Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer. 2011;11:404.
9. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47(1):8-32.

Use of non-US available products

10. Mehdizadeh M, Tavakoli-Aradakani M, Zamani S, Zamani G, Nikpour N. Evaluation of engraftment and adverse effects of granulocyte colony stimulating factor versus PEG granulocyte colony stimulating

factor in patients undergoing autologous hematopoietic stem cell transplantation. Iranian Journal of Pharmaceutical Sciences. 2021;17(1):99-106.
11. Li X, Zheng H, Yu MC, et al. Is PEGylated G-CSF superior to G-CSF in patients with breast cancer receiving chemotherapy? A systematic review and meta-analysis. Support Care Cancer. 2020;28(11):5085-5097.
12. Wang G, Zhang Y, Wang X, et al. Long-acting versus short-acting granulocyte colony-stimulating factors among cancer patients after chemotherapy in China: A systematic review and meta-analysis of randomized controlled trials. Medicine. 2021;100(51):e28218.
13. Esfandbod M, Agha Bararzadeh F, Faraz M, Zarrabi F, Toogeh G. Comparison of Long-Acting G-CSF (PD-Lasta) with Short-Acting G-CSF (PD-Grastim) in Neutrophil Recovery Following Consolidation Chemotherapy with High-Dose Cytarabine in Acute Myeloid Leukemia: A Randomized Clinical Trial. Int J Hematol Oncol Stem Cell Res. 2021;15(2):96-102.

Use of non-US labeled doses

14. Zhang W, Jiang Z, Wang L, Li C, Xia J. An open-label, randomized, multicenter dose-finding study of once-per-cycle pegfilgrastim versus daily filgrastim in Chinese breast cancer patients receiving TAC chemotherapy. Med Oncol. 2015;32(5):147.
15. Mahtani R, Crawford J, Flannery SM, Lawrence T, Schenfeld J, Gawade PL. Prophylactic pegfilgrastim to prevent febrile neutropenia among patients receiving biweekly (Q2W) chemotherapy regimens: a systematic review of efficacy, effectiveness and safety. BMC cancer. 2021;21(1):621.
16. Kubo K, Miyazaki Y, Murayama T, et al. A randomized, double-blind trial of pegfilgrastim versus filgrastim for the management of neutropenia during CHASE(R) chemotherapy for malignant lymphoma. Br J Haematol. 2016;174(4):563-570.
17. Bozzoli V, Tisi MC, Maiolo E, et al. Four doses of unpegylated versus one dose of pegylated filgrastim as supportive therapy in R-CHOP-14 for elderly patients with diffuse large B-cell lymphoma. Br J Haematol. 2015;169(6):787-794.
18. Sohn BS, Jeong JH, Ahn JH, et al. A pilot study on intermittent every other days of 5-dose Filgrastim compared with single Pegfilgrastim in breast Cancer patients receiving adjuvant Docetaxel, doxorubicin, and cyclophosphamide (TAC) chemotherapy. Invest New Drugs. 2020;38(3):866-873.

Wrong comparator

19. Wittman B, Horan J, Lyman GH. Prophylactic colony-stimulating factors in children receiving myelosuppressive chemotherapy: a meta-analysis of randomized controlled trials. Cancer Treat Rev. 2006;32(4):289-303.
20. Sung L, Beyene J, Hayden J, Nathan PC, Lange B, Tomlinson GA. A Bayesian meta-analysis of prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in children with cancer. Am J Epidemiol. 2006;163(9):811-817.
21. Li L, Ma S, Wu M, Tan X, Zhong S, Lang J. The prophylactic effects of long-acting granulocyte colony-stimulating factor for febrile neutropenia in newly diagnosed patients with epithelial ovarian cancer: a randomised controlled study. BMJ Support Palliat Care. 2019;9(4):373-380.
22. Kuderer NM. Meta-analysis of randomized controlled trials of granulocyte colony-stimulating factor prophylaxis in adult cancer patients receiving chemotherapy. Cancer Treat Res. 2011;157:127-143.
23. Berghmans T, Paesmans M, Lafitte JJ, Mascaux C, Meert AP, Sculier JP. Role of granulocyte and granulocyte-macrophage colony-stimulating factors in the treatment of small-cell lung cancer: a systematic review of the literature with methodological assessment and meta-analysis. Lung Cancer. 2002;37(2):115-123.

24. Sung L, Alibhai SM, Beyene J, et al. Hematopoietic colony-stimulating factor priming does not influence survival in acute myeloid leukemia: a meta-analysis of randomized trials. Leukemia. 2009;23(4):811-813.
25. Gupta AK, Meena JP, Haldar P, Tanwar P, Seth R. Impact of G-CSF administration post-allogeneic hematopoietic stem-cell transplantation on outcomes: a systematic review and meta-analysis. Am J Blood Res. 2021;11(5):544-563.
26. Leonard RC, Mansi JL, Keerie C, et al. A randomised trial of secondary prophylaxis using granulocyte colony-stimulating factor ('SPROG' trial) for maintaining dose intensity of standard adjuvant chemotherapy for breast cancer by the Anglo-Celtic Cooperative Group and NCRN. Ann Oncol. 2015;26(12):2437-2441.
27. Wang J, Zhan P, Ouyang J, Chen B, Zhou R. Prophylactic use of granulocyte colony-stimulating factor after induction chemotherapy in patients with newly diagnosed acute myeloid leukemia may increase the complete remission rate: a meta-analysis of five randomised controlled trials. Leuk Lymphoma. 2009;50(3):457-459.
28. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. Drugs. 2018;78(4):463-478.
29. Zeybek C, Gürsel O, Atay AA, Kürekçi AE, Özcan O. Effects of recombinant granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor on platelet aggregation in healthy volunteers. Rekombinant granülosit koloni-stimüle edici faktör ve granülosit-makrofaj koloni-stimüle edici faktörün sağlıklı gönüllülerde platelet agregasyonu üzerine Etkileri. 2015;35(2):112-117.

Wrong study design

30. Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer in the United Kingdom. Value Health. 2011;14(4):465-474.
31. Pettengell R, Bias P, Mueller U, Lang N. Clinical safety of tbo-filgrastim, a short-acting human granulocyte colony-stimulating factor. Support Care Cancer. 2016;24(6):2677-2684.
32. Mitchell S, Li X, Woods M, et al. Comparative effectiveness of granulocyte colony-stimulating factors to prevent febrile neutropenia and related complications in cancer patients in clinical practice: A systematic review. J Oncol Pharm Pract. 2016;22(5):702-716.
33. Lyman G, Lalla A, Barron R, Dubois RW. Cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. Curr Med Res Opin. 2009;25(2):401-411.
34. Kim MG, Han N, Lee EK, Kim T. Pegfilgrastim vs filgrastim in PBSC mobilization for autologous hematopoietic SCT: a systematic review and meta-analysis. Bone Marrow Transplant. 2015;50(4):523-530.
35. Kam G, Yiu R, Loh Y, et al. Impact of pegylated filgrastim in comparison to filgrastim for patients with acute myeloid leukaemia (AML) on high-dose cytarabine (HIDAC) consolidation chemotherapy. Support Care Cancer. 2015;23(3):643-649.
36. Gurion R, Shacham-Abulafia A, Shpilberg O, Raanani P. The use of myeloid colony-stimulating factors in hematologic malignancies: the role of systematic reviews and meta-analyses. Acta Haematol. 2011;125(1-2):68-79.
37. Godder KT, Henslee-Downey PJ. Colony-stimulating factors in stem cell transplantation: effect on quality of life. J Hematother Stem Cell Res. 2001;10(2):215-228.
38. Franco-Trigo L, Calleja-Hernandez MA, Garcia-Corpas JP. Treatment of febrile neutropenia: Filgrastim and pegfilgrastim. Ars Pharmaceutica. 2014;55(1):1-7.
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40. Dainiak N, Gent RN, Carr Z, 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;5(3):202-212.
41. Hirsch BR, Lyman GH. Pharmacoeconomics of the myeloid growth factors: a critical and systematic review. Pharmacoeconomics. 2012;30(6):497-511.
42. Kasper C, Zahner J, Sayer HG. Recombinant human erythropoietin in combined treatment with granulocyte- or granulocyte-macrophage colony-stimulating factor in patients with myelodysplastic syndromes. J Cancer Res Clin Oncol. 2002;128(9):497-502.
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44. Cortés de Miguel S, Calleja-Hernández M, Menjón-Beltrán S, Vallejo-Rodríguez I. Granulocyte colony-stimulating factors as prophylaxis against febrile neutropenia. Support Care Cancer. 2015;23(2):547-559.
45. Ghidini M, Indini A, Nigro O, et al. Advances in the pharmacological management of neutropenia in solid tumors: the advent of biosimilars. Expert opinion on pharmacotherapy. 2021;22(7):857-865.
46. Rapoport BL, Cooksley T, Johnson DB, Anderson R, Shannon VR. Treatment of infections in cancer patients: an update from the neutropenia, infection and myelosuppression study group of the Multinational Association for Supportive Care in Cancer (MASCC). Expert review of clinical pharmacology. 2021;14(3):295-313.
47. Foreman E. Biosimilars in supportive care. Current opinion in oncology. 2020;32(4):282-288.
48. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004;100(2):228-237.
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51. Gattu S, Wang J, Bellon A, Schelcher C, Nakov R, Arani R. Meta-analysis of Pharmacokinetic/Pharmacodynamic Results of 3 Phase 1 Studies with Biosimilar Pegfilgrastim. Clinical pharmacology in drug development. 2021;10(10):1130-1141.
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53. Morishita M, Leonard RC. Pegfilgrastim; a neutrophil mediated granulocyte colony stimulating factor-expanding uses in cancer chemotherapy. Expert Opin Biol Ther. 2008;8(7):993-1001.
54. Renwick W, Pettengell R, Green M. Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. BioDrugs. 2009;23(3):175-186.
55. Wang J, Li B. Chinese expert consensus on the application of pegylated recombinant human granulocyte colony-stimulating factor during concurrent chemoradiotherapy (2020 edition). Precision Radiation Oncology. 2021;5(1):4-11.

Appendix G: Supplemental Tables of Comparative Evidence

Table 1. Comparison of Included Randomized Trials among Systemic Reviews for Prophylaxis of Chemotherapy-induced Febrile Neutropenia

SR/comparator	RCT first author last name, year/comparator drug included in SR or SRMA												
Filgrastim vs pegfilgrastim (or similar)[a]													
PEG comparator	PEG	PEG	PEG	PEG	PEG	PEG	PEG	PEG	PEG	PEG	BIO PEG; NA	PEG	BIO PEG; NA
	Johnston 2000[b, 206]	Holmes 2002[c,170]	Holmes 2002[190]	Vose 2003[c,189]	Grigg 2003[c,191]	Green 2003[51]	Sierra 2008[c,d, 52]	Von Minckwitz 2008[195]	Fox 2009[42]	Sat-heesh 2009[e, 207]	Park 2013[c, 208]	Shi 2013 [209]	Salafet 2013[c, 210]
Rastogi et al 2021[44,f]		X	X	X	X	X					X		
Mohseni et al 2020[45]		X	X	X	X	X					X	X	X
Wang et al 2019[59]	X	X	X	X	X	X	X	X	X	X		X	
Cornes et al 2018[47,f]					X	X	X			X	X	X	X
Bond et al 2018[48]		X	X	X	X	X					X	X	
Filgrastim vs pegfilgrastim (or similar)[a], *continued*													
PEG comparator	PEG	PEG	EM-PEG; NA	Un-known PEG	PEG	BIO PEG; NA	Un-known PEG						
	Zhang 2015[c,211]	Bozzoli 2015[212]	Filon[213]; Nechaeva 2015[214]	Xu 2016[215]	Kubo 2016[216]	Park 2017[217]	Xie 2018[218]						
Rastogi et al 2021[44,f]	X				X	X							
Mohseni et al 2020[45]	X				X	X							

Table 1. Comparison of Included Randomized Trials among Systemic Reviews for Prophylaxis of Chemotherapy-induced Febrile Neutropenia

SR/comparator	RCT first author last name, year/comparator drug included in SR or SRMA												
Wang et al 2019[59]	X	X		X	X		X						
Cornes et al 2018[47,f]	X	X	X										
Bond et al 2018[48]													
Filgrastim vs filgrastim "biosimilar"[g]													
BIO comparator	TBO	TBO	TBO	AAFI	SNDZ	SNDZ	NA	SNDZ	SNDZ				
	del Giglio 2008[63]	Engert 2009[64]	Gatze-meier 2009[65]	Waller 2010[181]	Manko 2014[h, 60]	Black-well 2015[182]	Hegg 2016[219]	Blackwell 2018[183]	Har-beck 2018[i, 184]				
Rastogi et al 2021[44,f]	X			X		X	X	X					
Barbier et al 2020[185]		X	X			X							
Yang et al 2019[57]	X	X	X	X	X		X		X				
Wang et al 2019[59]	X	X	X	X		X	X						
Botteri et al 2018[58]	X			X		X	X						
Pegfilgrastim vs pegfilgrastim biosimilar													
BIO comparator	NA	NA	NA	BMEZ	BMEZ	JMDB	BIO PEG; NA	NA	NA				
	Park 2013[208]	Glaspy 2014[c, 220]	Zhou 2016[221]	Blackwell 2016[187]	Harbeck 2016[188]	Waller 2016[j, 186,196]	Park 2017[217]	Horvat-Karajz 2017[k, 222,223]	Desai 2018 [224]				
Yang et al 2019[57]	X		X	X	X			X	X				

Table 1. Comparison of Included Randomized Trials among Systemic Reviews for Prophylaxis of Chemotherapy-induced Febrile Neutropenia

SR/comparator	RCT first author last name, year/comparator drug included in SR or SRMA												
Wang et al 2019[59]		X		X	X				X				
Botteri et al 2018[58]				X	X	X	X						

Abbreviations: AAFI, filgrastim-aafi (Nivestym); AML, acute myelogenous leukemia; BIO, "biosimilar"; BMEZ, pegfilgrastim-bmez (Ziextenzo); EM-PEG, empegfilgrastim; G-CSF, granulocyte colony-stimulating factor; JMDB, filgrastim-jmdb (Fulphila); MA, meta-analysis; N, number of participants randomized to intervention; NA, not applicable – agent is not available in the US; PEG, pegfilgrastim; RCT, randomized controlled trial; TBO, tbo-filgrastim (Granix); SNDZ, filgrastim-sndz (Zarxio); SR, systematic review; SRMA, systematic review and meta-analysis

[a] Some studies allowed other pegylated G-CSF comparators (eg, a pegfilgrastim biosimilar) in MA comparison vs filgrastim; some of these products are not FDA-approved in the US. Additionally, while most studies described filgrastim as filgrastim, a few studies report origins of the products in other countries, so we cannot be sure that the product is the version available in the US/

[b] First small in-human study focused primarily on pharmacokinetics and safety

[c] Phase II RCT

[d] This study is in patients with AML with low to intermediate cytogenetics receiving induction and consolidation therapy

[e] This study is published as an abstract only and the abstract does not include a statistical analysis

[f] This study identified additional studies, but did not include all of them in the MA. The studies listed here are those included in 1 or more MA.

[g] Some studies included tbo-filgrastim as a biosimilar even though it is not approved as a biosimilar to filgrastim in the US

[h] This RCT was included in MA of CIN-related outcomes (patients did receive chemotherapy as part of their mobilizing regimen), but the primary outcome of the study is a comparison of the originator vs biosimilar for mobilization of CD34+ cells in the peripheral blood in patients with hematologic malignancies receiving an autologous HCT

[i] Safety analysis of 2 RCTs, one of which is Blackwell et al 2015

[j] Published abstract only for MA, but full text has been published (Waller et al 2019)

[k] Cited study is a published abstract (2017). Full text is published as of 2019 and also cited (Kahan et al 2019).

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
SRs or SRMAs primarily among patients with lymphoma/solid tumors receiving G-CSF for CIN prophylaxis[a]				
Rastogi et al 2021[225] SRMA *Quality of included studies*: most included studies considered to have low ROB (most common risk: lack of blinding)	Pubmed, Cochrane Database of SRs, Scholar, Clinicaltrials.gov (Inception to July 2020)	Any FDA-approved indication for FIL *FIL vs PEG* (1) CIN PP in solid tumor/lymphoma (9 RCTs) • Doses varied in studies: FIL (5 mcg/kg/day, or 50 to 100 mcg/m^2/day); PEG (30 – 100 mcg/kg/day or 3 mg – 6 mg/cycle) *FIL vs FIL biosimilar* (includes tbo-FIL) (2) CIN PP in breast cancer (5 RCTs)	(1a) FIL (n = 489) vs PEG (n = 508) (1b) FIL (n = 197) vs PEG (n = 203) (2a) FIL (n = 497) vs BIO (NR) (2b) FIL (NR) vs BIO (NR)	***Efficacy*** (random effects RR [95% CI]): (1a) FN incidence (9 RCTs, PEG vs FIL): 0.90 [0.67 to 1.12]; (I^2 = 52%, P = 0.42) (1b) Grade 3/4 neutropenia (3 RCTs, PEG vs FIL): 0.95 [0.81 to 1.12]; (I^2 = 39.6%, P = 0.55) (2a) Duration of SN (5 RCTs, FIL vs BIO): 1.03 (0.93 to 1.13); mean difference = – 0.37; (I^2 = 0.0%, P = 0.57) (2b) Proportion with FN (NR, FIL vs BIO): 0.87 (0.56 to 1.35); (I^2 = 0.0%, P = NR) ***Safety*** (AE mean frequency or RR [95% CI]): (1) Bone pain (4 RCTs): FIL = 6.7% (5% to 9%) PEG = 3.1% (0.4% to 5.8%); RR (FIL vs PEG): 0.56 (0.26 to 1.19) Other reported AEs: back pain, arthralgia, myalgia, thrombocytopenia, other "general toxicities" (2) Bone pain (NR): RR (FIL vs BIO): 1.18 (0.68 to 2.05) Myalgia events (NR): RR (FIL vs BIO): 1.05 (0.675 to 1.631)
Barbier et al 2020[185] SR *Quality* of included studies not formally assessed	Embase, Medline, Cochrane, Web of Science (Inception to June 2018)	*Switch* studies of a patient going from the reference biologic to biosimilar (approved in Europe) or *vice versa* For filgrastim, identified RCTs were for prophylaxis of CIN	Filgrastim vs tbo-filgrastim (2 single-switch RCTs) Filgrastim vs filgrastim-sndz (1 multiple-switch RCT)	***Conclusions about filgrastim vs tbo-filgrastim:*** similar safety and efficacy observed ***Conclusions about filgrastim vs filgrastim-sndz:*** Similar clinical characteristics when switching back and forth. "The immunogenic response showed no increased risk of developing ADA [anti-drug antibodies]."

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First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
Mohseni et al 2020[45] SRMA *Quality of studies:* Good (n = 3); moderate (n = 5); weak (n = 3)	Pubmed, Cochrane Library, Scopus, Embase, Web of Science (Inception to January 2018)	RCTs of patients with solid tumors or lymphoma receiving chemotherapy (and not other treatments that could cause neutropenia) receiving FIL or PEG for CIN prophylaxis Types of cancer: breast cancer, NHL, lymphoma, other solid tumors	(1) 11 RCTs; PEG (total n = 799) vs FIL (total n = 779) • Doses varied: PEG: 3.6 to 6 mg/cycle, or 100 mcg/kg/cycle; FIL: 50 to 100 mcg/m^2/day or 5 mcg/kg/day Not all RCTs were included in the MA	***Efficacy*** (random effects RR [95% CI]): (1a) FN incidence (PEG vs FIL): • *After cycle 1* (8 RCTs): 0.88 [0.66 to 1.16]; (I^2 = 0%, P = 0.35) • *All cycles* (7 RCTs): 0.76 [0.51 to 1.13]; (I^2 = 4%, P = 0.18) (1b) Incidence of grade 4 neutropenia after cycle 1 (7 RCTs, PEG vs FIL): 0.98 [0.91 to 1.06]; (I^2 = 0%, P = 0.66) (1c) Grade 4 neutropenia duration after cycle 1 (10 RCTs, PEG vs FIL): *mean difference: –0.02* [–0.18 to 0.15]; (I^2 = 0%, P = 0.86) (1d) Time to ANC recovery (PEG vs FIL): • *After cycle 1* (6 RCTs): *mean difference:* –0.03 [–0.34 to 0.29]; (I^2 = 0%, P = 0.87) • *All cycles* (3 RCTs): *mean difference:* –0.34 [–0.75 to 0.08]; (I^2 = 70%, P = 0.11) ***Safety*** (AE RR [95% CI]): (1e) Bone pain (9 RCTs, PEG vs FIL): 0.96 [0.79 to 1.17]; (I^2 = 12%, P = 0.68)
Yang et al 2019[57] SRMA *Quality of G-CSF studies*: moderate or low quality GRADE evidence	Pubmed, Embase, Cochrane Library, clinicaltrials.gov, Chinese databases (China National Knowledge Infrastructure, Wangfang, SinoMed), Conference abstracts from 2016 and 2018 meetings of the	Cancer patients receiving a biosimilar compared to the reference originator product (multiple types of products other than G-CSFs were included) Included cancers: BC, NSCLC, NHL; a small	(1) FIL vs biosimilar or tbo-filgrastim (~7 RCTs) (2) PEG vs biosimilar (~6 RCTs) Follow-up range: 3 to 30 weeks	***Efficacy*** (fixed effect RR [95% CI]): (1a) FN incidence after cycle 1 (4 RCTs, FIL BIO vs FIL): 1.09 [0.72 to 1.65]; (I^2 = 10.8%, P = 0.19, GRADE evidence = low) (1b) Duration of SN after cycle 1 (3 RCTs, FIL BIO vs FIL): *weighted mean difference:* 0.06 [–0.12 to 0.23]; (I^2 = 0%, P = 0.53, GRADE evidence = moderate)

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
	American Society of Clinical Oncology, ISI Web of Science, MedPage Today (Inception to December 2018)	number of other types in a trial of patients receiving a HCT (multiple myeloma, HL)		(2a) FN incidence after cycle 1 (4 RCTs, PEG BIO vs PEG): 1.14 [0.80 to 1.63]; (I^2 = 0%, P = 0.57, GRADE evidence = low) (2b) Duration of SN after cycle 1 (5 RCTs, PEG BIO vs PEG): *weighted mean difference:* 0.01 [–0.11 to 0.13]; (I^2 = 0%, P = 0.59, GRADE evidence = moderate) (2c) Time to ANC recovery after cycle 1 (6 RCTs, PEG BIO vs PEG): *weighted mean difference:* 0.07 [–0.10 to 0.24]; (I^2 = 5.8%, P = 0.43, GRADE evidence = moderate) ***Safety*** (AE RR [95% CI]): (1c) Bone pain (4 RCTs, possibly random effects analysis, FIL BIO vs FIL): 0.90 [0.78 to 1.05]; (I^2 = 51.3%, P = 0.18, GRADE evidence = moderate) (1d) Rate of ADE (4 RCTs, FIL BIO vs FIL): 1.03 [0.97 to 1.09]; (I^2 = 6.3%, P = 0.35, GRADE evidence = moderate) (2d) Rate of ADE (3 RCTs, possibly random effects analysis, PEG BIO vs PEG): 0.98 [0.95 to 1.01]; (I^2 = 61.8%, P = 0.16; GRADE evidence = moderate)
Wang et al 2019[59] SRMA and SRNMA *Quality of G-CSF studies*: most studies considered to have a low ROB by SR	Pubmed, Embase, Cochrane Library, Cochrane Collaboration Central Register of Controlled Clinical Trials, American Society of Clinical Oncology, ClinicalTrials.gov	Any cancer patients receiving G-CSF as prophylaxis after chemotherapy PEG vs FIL RCTs: primarily patients with BC; fewer patients with DLBCL, NSCLC,	(1) FIL vs PEG (16 RCTs, total n = up to 3399) • Doses varied: PEG: 30 to 300 mcg/kg/cycle (100 mcg/kg/cycle was most common), 3.6 mg – 6 mg/cycle	***Efficacy*** (random effects OR [95% CI]): (1a) FN incidence within 2 weeks after chemotherapy (16 RCTs, FIL vs PEG): **1.46 [1.07 to 1.99];** (I^2 = 8%) (1b) Incidence of SN (12 RCTs, FIL vs PEG): 1.07 [0.90 to 1.27]; (I^2 = 0%) (2a) FN incidence within 2 weeks after chemotherapy (4 RCTs, PEG vs PEG BIO): 1.12 [0.71 to 1.78]; (I^2 = 0%)

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
authors (about 20% of studies had a high-risk of bias due to random sequence allocation, and about 25% of studies with a high risk of bias due to lack of blinding)	(Inception to October 2018)	lymphoma, NHL, AML, or sarcomas PEG vs PEG BIO: BC patients FIL vs FIL BIO: primarily patients with BC; fewer patients with LC or NHL	FIL: 5 mcg/kg/day (most); 1: 300 mcg/day (2) PEG vs long-acting G-CSF (eg, PEG BIO) [4 RCTs, total n = up to 927] • Most studies: 6 mg/cycle vs 6 mcg/cycle; one study: PEG 6 mg/cycle, comparator 80 to 320 mcg/kg/cycle (3) FIL vs short-acting G-CSF (eg, FIL BIO or tbo-FIL) [6 RCTs, total n = up to 1371] • 5 mcg/kg/day vs 5 mcg/kg/day	(2b) Incidence of SN (1 RCT, PEG vs PEG BIO): 0.82 [0.46 to 1.47]; (I^2 = NA) (3a) FN incidence within 2 weeks after chemotherapy (6 RCTs, FIL vs FIL BIO): 1.04 [0.59 to 1.84]; (I^2 = 35%) (3b) Incidence of SN (3 RCTs, FIL vs FIL BIO): 0.94 [0.63 to 1.41]; (I^2 = NA) ***Safety*** (AE RR [95% CI]): (1c) Bone pain (11 RCTs, FIL vs PEG): 1.40 [0.81 to 2.40]; (I^2 = 46%) (2c) Bone pain (1 RCT, PEG vs PEG BIO): **1.43 [1.03 to 1.98];** (I^2 = NA) (3c) Bone pain (3 RCTs, FIL vs FIL BIO): **0.54 [0.30 to 0.99]**; (I^2 = 0%)
Cornes et al 2018[47] SRMA Most RCTs considered high-quality; 11/17 included RCTs were not blinded	Medline, Embase, Cochrane Library, conferences proceedings (2012 to 2015) for several relevant organizations (January 2003 to August 2015)	Adults (≥ 18 years) with a non-myeloid malignancy receiving chemotherapy or AML receiving induction/consolidation chemotherapy receiving G-CSF prophylaxis (excluding patients receiving G-CSFs before HCT)	PEG vs FIL (10 RCTs) • Doses varied: PEG: 60 mcg/kg to 120 mcg/kg single dose or 3.6 to 6 mg per cycle; FIL: 300 mcg daily, or 100 mcg/m^2/day, or 5 mcg/kg/day EMPEG vs FIL (2 RCTs)	***Efficacy*** (*fixed effect* RR [95% CI]): FN incidence (10 RCTs, *long-acting G-CSF [mostly PEG] vs short-acting G-CSF [mostly FIL]):* 0.86 [0.68 to 1.10]; (I^2 = 0%, P = 0.226) Incidence of hospitalizations: 5 RCTs reported no significant differences between long-acting and short-acting G-CSFs, but 2 of them "…reported a trend toward fewer hospitalizations for pegfilgrastim versus filgrastim"[47] (insufficient data for MA)

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
			Nonspecific pegylated G-CSF vs unpegylated daily G-CSF (5 RCTs) Not all RCTs were included in the MA	Dose reductions or delay in chemotherapy due to occurrence of neutropenia: 4 RCTs reported similar occurrences between short vs long-acting G-CSF groups (insufficient data for MA)
Botteri et al 2018[58] SRMA No included study quality assessment reported	Pubmed, clinical trial databases (clinicaltrials.gov, who.int/trialsearch, clinicaltrialsregister.eu) (inception to March 2017)	Breast cancer patients receiving the reference G-CSF vs its biosimilar	(1) FIL vs FIL biosimilar (including 1 study of tbo-FIL) [4 RCTs] • Blackwell 2015: FIL vs SNDZ (n = 214) • Waller 2010: FIL vs AAFI (n = 250) (2) PEG vs PEG biosimilar [3 RCTs] • Blackwell 2016: PEG vs BMEZ (n = 308) • Harbeck 2016: PEG vs BMEZ (n = 310) • Waller 2016: PEG vs JMDB (n = 194)	***Efficacy*** (mean difference [95% CI]); individual trial result because MA comparison is not relevant: (1a) Duration of SN after cycle 1, days (FIL BIO vs FIL): Blackwell 2015: –0.03 [–0.32 to 0.26] Waller 2010: 0.30 [0.01 to 0.59] (2a) Duration of SN after cycle 1, days (PEG BIO vs PEG): Blackwell 2016: 0.17 [–0.07 to 0.41] Harbeck 2016: –0.08 [–0.28 to 0.12] Waller 2016: 0.00 [–0.31 to 0.31] ***Safety*** (AE during any cycle, RR [95% CI]): *Fil BIO vs FIL:* (1b) Bone pain: Blackwell 2015: 0.87 [0.59 to 1.27] Waller 2010: 1.56 [0.94 to 2.59] (1c) Myalgia events: Blackwell 2015: 0.83 [0.26 to 2.65] Waller 2010: 1.50 [0.73 to 3.07] (1d) Serious AE events: Blackwell 2015: 3.0 [0.84 to 10.78] Waller 2010: 1.56 [0.52 to 4.70] *PEG BIO vs PEG:* (2b) Bone pain: Blackwell 2016: 0.58 [0.27 to 1.23] Harbeck 2016: 0.86 [0.32 to 2.33] Waller 2016: 1.12 [0.76 to 1.65] (2c) Myalgia events:

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
				Blackwell 2016: 0.68 [0.33 to 1.41] Harbeck 2016: 0.68 [0.30 to 1.55] Waller 2016: 2.64 [0.31 to 22.12] (2d) Serious AE events: Black well 2016: 0.89 [0.57 to 1.40] Harbeck 2016: 0.75 [0.41 to 1.39]
Bond et al 2018[48] SRMA and SRNMA *Formal quality assessment not reported*; included studies were phase 2/3 RCTs that were double-blinded or open-label. One study was a cross-over design.	Medline and Embase (2005 to 2015)	Adults with solid tumor or lymphoma receiving chemotherapy and G-CSF prophylaxis of neutropenic events (studies of G-CSFs for stem cell mobilization were excluded) PEG vs FIL comparison: most studies included patients with breast cancer or lymphoma (Hodgkins or NHL)	(1) PEG vs FIL (7 RCTs) • Doses varied: PEG: 3.6 or 6 mg/cycle, or 100 mcg/kg/cycle (most common) FIL: 5 mcg/kg/day (most common), or 100 mcg/m^2 (one study)	***Efficacy*** (random effects RR [95% CI]): (1a) FN incidence (6 RCTs, FIL vs PEG): **1.54 [1.03 to 2.29]**; (I^2 = 0%, **P = 0.04**) (1b) SN incidence after cycle 1 (5 RCTs, FIL vs PEG): 1.01 [0.93 to 1.10]; (I^2 = 0%, P = 0.83) (1c) SN incidence after cycles 2-4 (3 RCTs, FIL vs PEG): 1.17 [0.86 to 1.59]; (I^2 = 79%, P = 0.31) (1d) Time to ANC recovery (5 RCTs, FIL vs PEG): *mean difference: 0.*28 [–0.10 to 0.67]; (I^2 = 39%, P = 0.15) ***Safety*** (AE random effects RR [95% CI]): (1c) Bone pain (3 RCTs, FIL vs PEG): 1.05 [0.80 to 1.36]; (I^2 = 0%, P = 0.74)
Engert et al 2009[61] Patient-level data (ie, raw data and not summary statistics) MA of 3, phase 3 company-sponsored RCTs	No literature search. Included the 3 phase 3 randomized, double-blinded studies that "…represent the complete programme included cancer patients conducted with XM02 [tbo-filgrastim]"[61]	Adults (≥ 18) with a solid tumor or lymphoma who would be treated with chemotherapy requiring primary prophylactic support with a G-CSF Cancer type varied by RCT:	(1) Tbo-FIL (total n = 363) vs FIL (total n = 245), both at 5 mcg/kg/d subQ starting 1 day after chemotherapy for a at least 5 days and a max of 14 days (stopped when post-nadir ANC reached ≥10 x 10^9/L) during chemotherapy cycle 1	***Efficacy*** (1a) Incidence of FN in cycle 1 (% [95%CI], TBO-FIL vs FIL): • BC: 12.1% (7.7% to 18.6%) vs 12.5% (8% to 19.1%); *difference* (TBO-FIL *minus* FIL): –0.4% (–8.3% to 7.5%) • LC: 15% (10.3% to 21.3%) vs 8.8% (4.3% to 17%); *difference* (TBO-FIL *minus* FIL): 6.3% (–3.2% to 14%)

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
		High-risk stage II-IV BC (Del Giglio 2008) NSCLC (Gatzmeier 2009)[65] Aggressive NHL (Engert 2009)[64] (Details of this studies, are included in **Table 3** below)		• NHL: 11.1%% (5.5% to 21.2%) vs 20.7% (9.8% to 38.4%); *difference* (TBO-FIL *minus* FIL): –9.6% (–28.2% to 5.2%) *Weight arithmetic mean risk difference [95%CI] of the 3 trials:* 1.7% (–3.8% to 7.1%) *Odds ratio [95%CI] for the combined incidence of FN, adjusted by study (TBO-FIL vs FIL):* 1.08 (0.66 to 1.77) (1b) FN incidence in cycle 1, adjusted for myelosuppressive chemotherapy potency: *Weight arithmetic mean risk difference [TBO-FIL minus FIL, 95%CI] of the 3 trials: 0.6%* (–5.0% to 6.2%) *Odds ratio [95%CI] for the combined incidence of FN, adjusted by study (TBO-FIL vs FIL):* 1.08 (0.66 to 1.78) ***Safety:*** No data reported Author conclusion: "XM02 [tbo-FIL] is non-inferior to the reference medication [FIL], regardless of the myelotoxic potency of the applied chemotherapy regimens"[61]
SRs or SRMAs primarily among patients receiving G-CSFs primarily as neutrophil recovery support following an auto-PBSCT[b]				
Busca et al 2018[55] SR Quality not formally assessed; 3 RCTs were open-label (Sebban 2012, Rifkin 2010, Cesaro	Pubmed and Cochrane Register of Controlled Trials (2005 to 2016)	Focus on patients with hematologic malignancies receiving G-CSF/or granulocyte transfusions as prophylaxis or treatment; allowed any study design	(1) FIL vs PEG after auto-HCT for NHL/HL/MM, adults (3 RCTs; FIL [total n = 144; PEG [total n = 145] *FIL:* 5 mcg/kg/day until ANC recovery (2 RCTs); or strata-based doses (300 mcg for <60 kg; 480 mcg for 60-96 kg; 780 mcg for >96 kg) *PEG:* 6 mg single dose	***Efficacy*** (1) Similar efficacy between PEG and FIL for days of moderate-severe neutropenia/neutropenia days (2 RCTs), days with fever (1 RCT), rate of fever of unknown origin (1 RCT), documented infection (1RCT), bacteremia rate (1 RCT), hospitalization days, and days with IV antibiotics (2 RCTs) • 1 RCT with conflicting result (Martino et al), which found PEG > FIL for reducing the incidence and duration of severe

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
2013); Martino et al did not report blinding information; others were double-blinded		For PEG vs FIL, RCTs were among: Auto-PBSCT for NHL/HL/MM, Adults (Sebban 2012, phase II trial)[176] Auto-PBSCT for MM, Adults (Martino 2006)[177] Adult AML (Sierra 2008, phase II trial)[52] Auto- PBSCT for NHL, adults (Rifkin 2010, phase II trial)[178] Auto- PBSCT for solid tumors or NHL/HL, Pediatrics (Cesaro 2013, phase III trial)[43] NHL/HL, adults (Kubo 2016, phase III trial)[216]	(2) FIL vs PEG after auto-HCT for solid tumor/NHL/HL, pediatrics (1 RCT; FIL [n=29]; PEG [n=32]) *FIL*: 5 mcg/kg/day for ≥ 9 days *PEG*: 100 mcg/kg single dose (3) FIL vs PEG for adult AML (1 RCT; FIL [n=41]; PEG [n=42] *FIL:* 5 mcg/kg/day until ANC recovery *PEG:* 6 mg single dose (4) FIL vs PEG for CIN prophylaxis in NHL/HL (1 RCT); FIL [n=55]; PEG [n=54] *FIL*: 50 mcg/m^2 daily, to ANC recovery *PEG*: 3.6 mg single dose *All doses given subQ* or route not specified (Cesaro et al)	neutropenia. However, this study started PEG 24 hours after HCT vs FIL on day 5 after HCT. (2) Similar efficacy between PEG and FIL for incidence of FN and documented infections (3) Similar efficacy between PEG and FIL for incidence of FN (4) PEG > FIL for reduction in severe neutropenia, but similar efficacy for incidence of FN Overall conclusion by authors: "peg-filgrastim is at least as effective as filgrastim in adult and pediatric auto-PBSC [autologous peripheral blood stem cell transplantation] and in adult NHL, HL and AML"[55] ***Safety*** No assessment by study authors
Ziakas et al 2012[56] SRMA RCTs were rated as at least A; two RCTs were rated as A+ due to being multicenter	Medline, Embase, Cochrane Registry of Randomized Controlled Trials (Inception to February 2011)	Use of FIL or PEG for support after auto-HCT; allowed any study design RCTs were among:	(1) FIL vs PEG after auto-PBSCT (4 RCTs, total n: FIL = 146, PEG = 147) • FIL: 5 mcg/kg/day (or based on weight strata in 1 trial: 300 mcg for <60 kg; 480 mcg for 60-96 kg;	***Efficacy*** (MA combined randomized and retrospective studies, so individual RCT results are reported) (1a) ANC recovery to >0.5x10^9/L, days (PEG vs FIL, mean (SD); *mean difference* [95%CI]): Martino 2006: 5 (3) vs 6 (1.5); –1 [–2.54 to 0.54] Gerds 2010: 9 (1.25) vs 10 (1.75); –1 [–1.67 to –0.33]

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
and/or double-blinded		Auto-PBSCT for MM, adults (Martino 2006; A quality)[177] Auto-PBSCT for MM, lymphoma, testicular or ovarian carcinoma, adults (Gerds 2010, double-dummy, phase III trial; A+ quality)[180] Auto-PBSCT for hematologic malignancies or solid tumors, adults (Castagna 2010, open-label noninferiority trial; A+ quality)[179] Auto-PBSCT for NHL, adults (Rifkin 2010, phase II trial; A quality)[178]	780 mcg for >96 kg) subQ and typically until sustained neutrophil engraftment (eg, ANC 5 x 10^9/L for 3 days)[178,180] or ANC recovery (eg, ANC >0.5 x 10^9/L for 2 days)[179] • PEG: 6 mg single dose subQ Both were started ~24 hours post-PBSC infusion, except for the Martino et al study where FIL was started on day +5 vs day +1 for PEG, after PBSC infusion • Range of number of FIL injections: 6[177] to 12.6[178]; 3/4 RCTs with injection number ≥ 10	Castagna 2010: 10.75 (4.61) vs 11.53 (5.58); –0.78 [–3.02 to 1.46]; *noninferiority met* Rifkin 2010: 9.3 (1.1) vs 9.8 (1.3); –0.50 [–0.98, –0.02]; *noninferiority met* *Individual studies reported similar time to neutrophil recovery between groups*. The MA including non-randomized studies significantly favored PEG over FIL by ~0.8 days. (1b) Other efficacy measures (PEG vs FIL; varied by trial): • Gerds/Castagna/Rifkin: no significant differences in duration of fever (1 vs 2 d; 0.95 vs 1.63 d; or 7.1 vs 6.9 d). Martino reported longer length with FIL (1.5 vs 4 d). • Gerds/Castagna/Martino: no significant differences in hospitalization length • Rifkin and Castagna reported a similar risk of FN (18% vs 16.7%; and 56% vs 62%) whereas Martino et al reported a significantly higher risk of FN with FIL (61.1% vs 100%) • Similar time to platelet engraftment (Gerds, Martino), number of platelet transfusions (Gerds, Matino), number of RBC transfusions (Rifkin, Castagna, Martino) and RBC transfusion units (Rifkin and Castagna) Overall SR conclusion: "Overall pegfilgrastim was comparable to filgrastim with a marginal benefit (one d) in neutrophil recovery and in duration of FN. There was no effect on the risk of FN or the LOS [length of stay]."[56] ***Safety*** (1c) Bone pain:

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First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
				Rifkin: 1 patient in PEG group (vs none in FIL group) reported severe pain Martino (PEG vs FIL): 10% vs 12% (1d) Grade 3 or 4 AE: Gerds: no events attributable to either drug (1e) Severe mucositis (PEG vs FIL) Gerds (median): 1 vs 0, P = 0.44 Castagna: 60% vs 51%, P = 0.44 (1f) Most common AE (PEG vs FIL): Rifkin: neutropenia (40% vs 33%), thrombocytopenia (46% vs 37%), FN (18% vs 17%), infection (14% vs 17%), anemia (12% vs 21%) [few events considered drug-related]
SR or SRMAs among people receiving G-CSFs for peripheral blood stem cell mobilization[c]				
Kuan et al 2017[53] SRMA ROB assessment by outcome: overall *low* ROB for primary outcome of successful mobilization, though the risk of other bias was considered high; QOE assessment by outcome: *low QOE* for successful	Medline/Medline in-process, Embase, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Database of abstracts of reviews of effect, Health Technology Assessment database, NHS Economic Evaluation database, abstracts from American Society of Clinical Oncology and American Society of Hematology Meeting abstracts	People receiving either pegylated G-CSF (eg, PEG) or non-pegylated G-CSF (eg, FIL) for PBSC mobilization Included RCTs for PEG vs FIL were all in the setting of auto-HCT; type of cancer varied by study (when reported): Not reported (Bouko 2013[226]) Sarcomas, primarily in children (Fox 2009[42])	(1) PEG vs FIL for PBSC mobilization in auto-HCT (6 RCTs; FIL total n =148; PEG total n = 266) • Doses and timing varied: FIL: 5 to 10 mcg/kg/day, with variable start times (range ~1 day to day 5), and continued to various targets (either last day or apheresis or until reaching a target ANC count) PEG: single fixed-dose (6 mg, 12 mg, or 18 mg) given at variable start times (day 3 to	***Efficacy*** (random effects RR [95% CI]): (1a) Successful mobilization, PEG 6 mg given 24-48h after chemotherapy vs FIL 5 mcg/kg/day (2 RCTs, Kuan 2015 and Russell 2008): 0.87 [0.67 to 1.11]; (I^2 = 0%, P = 0.26) Discussion of other outcomes (insufficient data for MA): (1b) Quantity of collected CD34+ cells (3 RCTs) 3 RCTs (Bouko, Kuan, Russell) report similar quantity with PEG (6 mg) vs FIL (5 mcg/kg/day) (1c) Number of required apheresis procedures for successful mobilization (2 RCTs with details): Kuan and Russell report 78-85% of patients were successful with ≤ 2 apheresis after either FIL 5 mcg/kg/d or PEG

Table 2. Summary of Direct Comparative Evidence from Systematic Reviews and Meta-analysis

First author, year, study design	Databases searched (literature search date)	Population	Treatment Comparison (n)	Results
mobilization; *very low QOE* for AE and other efficacy outcomes	(January 2000 to May 2015); Clinical trial databases (as of May 26, 2015): clinicaltrials.gov, WHO International Clinical Trials Registry Platform, EU Clinical Trial Register, Controlled Clinical Trials	Lymphoma, myeloma or acute leukemia, adults (Kuan 2015[42]) NHL, adult (Russell 2008; phase II trial[227]) Solid tumors, adult (Willis 2009[228]) NSCLC, adult (Johnston 2000) Two additional included RCTs used a non-PEG comparator (Viens 2002[229]), or non-FIL comparator (Mele 2009[230])	day 7), or as a weight-based single dose (30 to 100 mcg/kg) started ~24 to 36 hrs after chemotherapy All studies except one (Bouko) used G-CSFs combined with chemotherapy for mobilization. Bouko et al looked at mobilization with G-CSF alone.	(1d) Peak peripheral blood CD34+ cells (6 RCTs): comparable between FIL and PEG when used at roughly equivalent doses (1e) auto-HCT survival: not reported (1f) Time to neutrophil and platelet engraftment (2 RCTs): similar time observed with PEG vs FIL (Kuan, Russell) ***Safety*** (AE random effects RR, PEG vs FIL [95% CI]): *Exact studies used in MA not reported. One included study used a non-PEG long-acting G-CSF.* (1g) Total bone pain incidence (3 RCTs): 0.86 (0.34 to 2.17) (1h) Total back pain incidence (2 RCTs): 0.84 (0.53 to 1.32) (1i) Total arthralgia incidence (2 RCTs): 0.69 (0.20 to 2.42)

Abbreviations: AAFI, filgrastim-aafi (Nivestym); ADE, adverse drug event; AE, adverse events; AML, acute myelogenous leukemia; auto-HCT, autologous hematopoietic stem cell transplant; BC, breast cancer; BIO, biosimilar; BMEZ, pegfilgrastim-bmez (Ziextenzo); CI, confidence interval; CIN, chemotherapy-induced febrile neutropenia; DLBCL, diffuse large B-cell lymphoma; FIL, filgrastim; FN, febrile neutropenia; G-CSF, granulocyte colony stimulating factor; HCT, hematopoietic cell transplant; H-H, direct head-to-head comparison; JMDB, filgrastim-jmdb (Fulphila); LC, lung cancer; n, number of participants randomized to intervention; NHL, non-Hodgkin's lymphoma; NA, not applicable; NR, not reported; OR, odds ratio; NSCLC, non-small-cell lung carcinoma; PBSCT, peripheral blood stem cell transplantation; PEG, pegfilgrastim or long-acting G-CSF; PP, primary prophylaxis; RCT, randomized controlled trial; ROB, risk of bias; RR, risk ratio; SN, severe neutropenia (ie, usually grade 4 neutropenia); SNDZ, filgrastim-sndz (Zarxio); SRMA, systematic review and direct meta-analysis; TBO-FIL, tbo-filgrastim (Granix); QOE, quality of evidence;

[a] FIL and PEG abbreviations refers to filgrastim- or pegfilgrastim-like products, unless described specifically as a biosimilar product. Reporting of the exact origin of the product used was variable in studies of PEG vs FIL, and some may have included a similar product in place of the US filgrastim or pegfilgrastim product.

[b] FIL and PEG abbreviations refers to filgrastim- or pegfilgrastim-like products. Product origin was not reported by each study, but about half reported US- or European-produced originator products.

[c] FIL and PEG abbreviations refers to filgrastim- or pegfilgrastim-like products. Product origin was not reported by each study, but most reported US-produced originator products.

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
Filgrastim vs pegfilgrastim for CIN PP[a]			

Green et al 2003[51]
 	
Phase 3, NI, RDBCT, multi-country including Europe, USA, and Australia
	Adults (≥ 18 years) with "high-risk" stage II or stage III/IV BC receiving DD x 4 cycles
	
	G-CSF administered approximately 24 hrs after completing chemo in each cycle
		FIL (n = 75)
		5 mcg/kg/day subQ, continued until ANC ≥ 10 x 10^9/L after nadir or max of 14 days
		
		vs
		
		PEG (n = 77)
		6 mg/cycle subQ (+ daily PBO injections continued until ANC ≥ 10 x 10^9/L after nadir or max of 14 days)
			Efficacy
			Primary endpoint
			Mean duration of SN (grade 4 neutropenia, ANC <0.5 x 10^9/L) after cycle 1 (FIL vs PEG): 1.6 days vs 1.8 days (mean difference: 0.23, 95%CI –0.15 to 0.63)
			• **NI established** if upper limit of CI for difference is <1 day
			
			Secondary endpoints
			Mean duration of SN (grade 4 neutropenia, ANC <0.5 x 10^9/L) in cycles 2-4 (FIL vs PEG): numerically shorter durations vs cycle 1 in both groups; no significant differences between treatment groups
			• Similar time to ANC recovery (9 days) in both groups
			
			Other endpoints
			Incidence of FN (PEG vs FIL, cycle 1): 9% vs 15%
			Incidence of FN (PEG vs FIL, any cycle): 13% vs 20% (difference: –7%, 95%CI –19% to 5%)
			• FN definition = oral temp ≥ 38.2 degC + ANC ANC <0.5 x 10^9/L
			
			% of patients receive IV antibiotics (PEG vs FIL): 21% vs 17%
			% of patients hospitalized (PEG vs FIL): 31% vs 18%
			
			Safety
			• Any drug-related AE (%, PEG vs FIL): 57% vs 58%
			• Most common drug-related AE (%, PEG vs FIL): 37% vs 42%; mostly mild; severe bone pain (%, PEG vs FIL): 1% vs 8%)
			• Serious AE:
			  ○ FIL: 2 events: pneumonitis, ARDS (resulted in death)
			  ○ PEG: 1 event: hypoxia and chest pain
			• Laboratory AE: reversible, temporary increases in ALP, LDH and uric acid; grade 4 anemia, grade 4 thrombocytopenia

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
Sierra et al 2008[52] Phase 2, multicenter (Australia, Europe, North America), RDBCT Study was stopped early due to apparent benefit, but a programming error occurred. Regardless, investigators state there was an adequate sample size. 50% of patients in each arm completed the study	Adults (≥ 18) with *de novo* AML (some unfavorable cytogenetic types were excluded) with a life expectancy of at least 3 months and no previous AML treatment. 81%-93% of patients classified as 'intermediate' cytogenetics, others were 'favorable', with 1 'unfavorable' accidentally included Chemotherapy: Induction 1: IA 3+7 (idarubicin days 1-3 + cytarabine twice daily on days 1-7) Induction 2: only given if needed Consolidation (given when ≤5% myeloblasts): High-dose cytarabine twice daily on days 1, 3, 5 *All patients completed induction 1 (4*	FIL (n = 41) + comparator-matched PBO 5 mcg/kg subQ started 24 hours after chemo and continued until post-nadir ANC reach ≥ 1 x 10^9/L x 3 days in a row, or ≥ 10 x 10^9/L x 1 day *Median number of doses:* 16 (induction 1) and 13 (consolidation) vs PEG (n = 42) + comparator matched PBO 6 mg single-dose subQ 24 hours after chemo + matched PBO given per ANC recovery like FIL The assigned G-CSF intervention was given during every chemotherapy course (total duration = max of 3 months + 1 month follow-up)	***Efficacy*** *Primary endpoint* (analyzed by Kaplan-Meier methods with censoring for patients that patients without ANC recovery [withdrawal, start of next chemo cycle, or failed recovery]): Median time to SN (ANC <0.5 x 10^9/L) recovery (duration from day 1 of chemotherapy until 2 consecutive ANC values ≥ 0.5 x 10^9/L) during **induction 1** [PEG vs FIL]: 22 days vs 22 days (*difference:* 0.0, 95%CI –1.9 to 1.9 days) 83% of patients in PEG arm vs 78% of patients in FIL arm with ANC recovery Median time to SN (ANC <0.5 x 10^9/L) recovery (duration from day 1 of chemotherapy until 2 consecutive ANC values ≥ 0.5 x 10^9/L) during **consolidation** [PEG vs FIL]: 17 days vs 16.5 days (*difference:* 0.5, 95%CI –1.1 to 2.1 days) 82% of patients in PEG arm vs 96% of patients in FIL arm with ANC recovery *Selected other outcomes* (PEG vs FIL) Remission rate after induction 1 or 2 chemotherapy: 79% vs 68% (95% CI for difference: –9% to 29%) Incidence/duration of hospitalization and nonprophylactic IV antimicrobials: *Hospitalization:* similar in both arms (nearly all in both, per usual care) *IV antimicrobials during induction 1:* given to all except 2 FIL patients; mediation duration: 18.5 vs 21 days *IV antimicrobials during consolidation:* 82% vs 67%; mediation duration: 21 vs 21.5 days Incidence and duration of FN (ANC <0.5 x 10^9/L and oral temp ≥ 38°C): *During induction 1*: 81% vs 88%; median duration: 15 days vs 14 days Incidence and duration of fever (oral temp ≥ 38°C): *During induction 1:* 90% vs 93%; median duration: 5 days vs 6 days *During consolidation:* 17/22 (77%) vs 14/24 (58%); mediation duration: 2 days each

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
	completed induction 2); 54.8% completed consolidation		PEG PK: Tracked PEG serum concentrations, and determine they exceeded the "clinically relevant threshold (2 ng/mL, derived from modeling)" for the duration of neutropenia in the study (ie, about 21 days) ***Safety* (% PEG vs % FIL)** • Treatment-related AE: 26% vs 22%; 1 serious AE (vascular purpura – PEG arm) and 3 non-treatment related deaths (1 PEG, 2 FIL) • D/c due to AE: 5% vs 5% • Types of AE not reported, but described as expected for AML treatment and similar between study arms
Fox et al 2009[42] Noninferiority, ROLCT at 2 sites in the US	Children and young adults (age <26 years; median age of 20, range: 3.8 to 25.8) a newly diagnosed sarcoma without prior receipt of chemo or radiation and without bone barrow involvement of the sarcoma G-CSF administered approximately 24 hrs (FIL) or 24-36 hrs (PEG) after completing chemo in each cycle 14, 21-day cycles planned (6 V_3DC + 9 IE) + surgery/radiation after cycle 5	FIL (n = 17) 5 mcg/kg/day subQ, continued until ANC ≥ 10,000/mcL after nadir Median number of doses: 13 (for V_3DC cycles) or 10 for (IE cycles) vs PEG (n = 17; 2 patients did not complete cycles 1-4) 100 mcg/kg/cycle single-dose subQ	***Efficacy*** *Primary endpoint* Median duration of SN (ANC < 500/mcL) during cycles 1-2 (V_3DC) and cycles 3-4 (IE) [PEG vs FIL]: *Data only available for 28/34 enrolled patients* V_3DC cycles: 5.5 (range 3-8) days vs 6.0 (range 0-9) days; P =0.76 IE cycles: 1.5 (range 0-4) vs 3.75 (range 0-6.5); P=0.11 *Noninferiority to be established if duration of SN was no longer than 1 SD for PEG compared to FIL, but they did not present this info, perhaps due to skewed data. Authors concluded they are similar for this outcome, but some of the evidence numerically favors PEG (eg, number of infections).* *Other outcomes* • No dose reductions or delays in either treatment arm • PK: no PEG neutralizing antibodies detected; absorption and clearance parameters significantly differed between PEG and FIL arms Median pre-nadir ANC peak: Significantly higher in PEG vs FIL arm (20,100/mcL vs 10,700/mcL; P=0.024) Median post-nadir ANC peak: Significantly higher in PEG vs FIL arm (8,000/mcL vs 20,400/mcL; P<0.001)

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
	• Cycles 1&2: V_3DC • Cycles 3&4: IE		Grade 3 fever and neutropenia with hospitalization during cycles 1-4 (PEG vs FIL): 12/17 (29% cycles) vs 15/17 (47% cycles) Documented infections (PEG vs FIL): 4 vs 8 Median count of mobilization of stem (CD34+) cells in cycle 1 (PEG vs FIL): 165/mcL vs 53 mcL (P=0.97) ***Safety* (for all patients/cycles: PEG (17/63) vs FIL (17/68):** • Grade ≥ 2 mucositis: 4/4 vs 7/9 • Grade ≤ 2 bone pain: 3/4 vs 3/3 • Grade ≤ 2 ↑ hepatic transaminases: 6/7 vs 5/8 • Grade 3 ↑ hepatic transaminases: 1/1 vs 1/1
Filgrastim vs pegfilgrastim for mobilization of PBSC for auto-HCT[b]			
Skopec et al 2017[54] Single-site in Slovenia, RCT Lacked details about any blinding. Also no power calculation reported.	Adults with newly diagnosed MM planning for CSF-only mobilization for auto-HCT and that completed treatment with 3-6 cycles of bortezomib + dexamethasone	FIL (n = 21; 1 did not complete HCT and was excluded from analysis) ~10 mcg/kg/day subQ, day of start not reported. Continued until reaching PB CD34+ target. vs PEG (n = 21; 2 did not complete HCT and was excluded from analysis) Single subQ dose of 12 mg on day 1	***Efficacy* (**primary outcome not specified but may be collected PBSCs based on reported statistical analysis plan): Median number of collected PBSC (FIL vs PEG): 5.05 x 10^6/kg vs 4.66 x 10^6/kg (P=0.428) Median number of apheresis procedures (FIL vs PEG): 2.5 (range 1-4) vs 2 (range 1-5), P=0.901 Sub-analysis of total WBC on day 1 of apheresis and median PBSCs in PB and apheresis product: Similar median counts observed between arms Sub-analysis of type of precursor cell (ie, lymphoid, myeloid, or megakaryoid) on day 1 of apheresis: Similar median counts between arms in both peripheral and apheresis blood *except* for a higher median number of megakaryoid precursor cells in the PB (P=0.027), although similar numbers were observed in the apheresis product. Neutrophil and platelet engraftment after transplant (FIL vs PEG): 1. Median time for neutrophils: 13 vs 16.5 days 2. Median time for platelets: 13 vs 16 days

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
		Both arms: Apheresis was performed when PB CD34+ cells reached 15 x 10^6/L. Patients received a melphalan conditioning regimen before auto-HCT and FIL 5 mcg/kg/d starting on day 9 post auto-HCT and until neutrophil engraftment	(median infused PBSC dose was similar, but slightly higher numerically in FIL vs PEG arm: 2.44 vs 2.37 x 10^6/L) ***Safety*** Comparative safety not clearly reported • No grade 3 or 4 AE in either arm • No leukocytosis >100 x 10^6/L in either arm
Filgrastim vs tbo-filgrastim for CIN PP			
Del Giglio et al 2008[63] Phase 3 RSBCT, multi-country in Europe, South America, and South Africa	Adult (≥ 18 years), "high-risk" Stage II, or stage III-IV BC receiving DD for 3 week cycles x 4 cycles max G-CSF administered approximately 24 hrs after completing chemo	FIL (n = 136) vs TBO-FIL (n = 140) Both: 5 mcg/kg/day subQ, continued until ANC ≥ 10 x 10^9/L after nadir for min of 5 days or max of 14 days Included additional PBO arm (n = 72) that switched to TBO after cycle 1	***Efficacy*** *Primary endpoint* Mean duration of SN (grade 4 neutropenia, ANC <0.5 x 10^9/L) after cycle 1 (TBO vs FIL): 1.1 days vs 1.1 days (difference: 0.028, 95%CI –0.261 to 0.316) • **Equivalence established** if 95% CI for the difference was within ± 1 day • Superiority of TBO over placebo (3.9 days) established *Secondary endpoints* Incidence of FN (FN = temp >39.5°C for ≥ 1 hr and ANC <0.5 x 10^9/L on same day or per-protocol, requiring antibiotic use); % TBO vs FIL in cycle 1: 12.1% vs 12.5% Incidence of FN (% TBO vs FIL during any cycle): 20.7% vs 22.1% Mean duration of SN in cycles 2-4: shorter durations vs cycle 1 observed, with similar durations between groups Mean ANC nadir depth in cycle 1 (10^9/L), TBO vs FIL: 0.7 vs 0.7 (difference: –0.001, 95%CI –0.190 to 0.189) Time to ANC recovery in cycle 1, TBO vs FIL: 8.0 days vs 7.8 days (difference: 0.207, 95%CI –0.425 to 0.838) ***Safety* (selected AE):** • D/c drug due to AE (%, TBO vs FIL vs PBO/TBO): 1.4% vs 2.2% vs 5.6% (reasons included sepsis, ischemic stroke, cardiac/respiratory arrest, syncope, pulmonary

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
			infarction, hyperglycemia/myalgia, increased ALT or AST, thrombocytopenia). No deaths considered drug-related. • Most common drug-related AE: bone pain (10.3%), asthenia (7.8%), myalgia (6.3%), diarrhea (5.2%) • Similar AE profile between TBO and FIL except for total incidence of AE across all cycles (%, TBO vs FIL): 25.7% vs 39.7%, P = 0.0149 • Immunogenicity: few anti-drug Ab detected; no confirmed neutralizing Ab Overall TEAE: 94.5% with AE, 29.9% considered severe ***Pharmacokinetics*** Similar PK properties observed between TBO and FIL
Engert et al 2009[64] Phase 3 RSBCT multi-country *Switch study* (patients switch to TBO-FIL after FIL initially)	Adults (age ≥ 18) with "aggressive" NHL receiving CHOP ± R every 3 weeks G-CSF administered approximately 24 hrs after completing chemo • Randomization during cycle 1 only (all participants received TBO after cycle 1)	FIL (n = 29) vs TBO-FIL (n = 63) Both: 5 mcg/kg/day subQ, continued until ANC ≥ 10 x 10^9/L after nadir for min of 5 days or max of 14 days	***Efficacy*** *(study focus was safety, efficacy analyses considered exploratory)* Mean duration of SN (grade 4 neutropenia, ANC <0.5 x 10^9/L) after cycle 1 (TBO vs FIL): 0.5 days versus 0.9 days (P=0.1055) Incidence of FN (temp > 38.5°C for ≥ 1 h + ANC <0.5 x 10^9/L on same day) after cycle 1 (TBO vs FIL): 11.1% vs 20.7% (P = 0.1232) Mean ANC nadir [10^9/L] cycle 1 (TBO vs FIL): 1.7 vs 1.1 (P = 0.1531) Mean time to ANC recovery after cycle 1 (TBO vs FIL): 6.0 days vs 6.7 days (P = 0.4939) ***Safety*** **(selected drug-related TEAE during cycle 1)** • Bone pain (%, TBO vs FIL): 6.3% vs 0% • Arthralgia (%, TBO vs FIL): 3.2% vs 3.4% • Bain pain (%, TBO vs FIL): 0% vs 3.4% • MSK pain (%, TBO vs FIL): 0% vs 3.4% • Pyrexia (%, TBO vs FIL): 3.2% vs 0% • Fatigue or flu-like illness (%, TBO vs FIL): 3.2% each vs 0% • Headache: 1.6% vs 0% • Diarrhea (%, TBO vs FIL): 3.2% vs 0% • Anemia (%, TBO vs FIL): 0% vs 3.4%

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
			Overall TEAE: 88% with AE, 17.4% considered severe ***Pharmacokinetics*** Similar PK properties observed between TBO and FIL
Gatzemeier et al 2009[65] Phase 3, multi-country, RCT *Switch study* (patients switch to TBO-FIL after FIL initially)	Adults (≥ 18 years) with small-cell or non-small-cell lung cancer receiving platinum-based chemotherapy (up to 1 previous chemotherapy regimen was allowed) for a max of 6 cycles with a cycle length of 3-4 weeks G-CSF administered approximately 24 hrs after completing chemo • Randomization during cycle 1 only (all participants received TBO after cycle 1)	FIL (n = 80) vs TBO-FIL (n = 160) Both: 5 mcg/kg/day subQ, continued until ANC ≥ 10 x 10^9/L after nadir for min of 5 days or max of 14 days	***Efficacy*** *(study focus was safety, efficacy analyses considered exploratory)* Mean duration of SN (grade 4 neutropenia, ANC <0.5 x 10^9/L) after cycle 1 (TBO vs FIL): 0.5 days versus 0.3 days; *difference (TBO minus FIL):* 0.157 days (95% CI –0.114, 0.428 days). *Authors considered this to be as the CI is within ± 1 day, yet efficacy analyses were exploratory; similar results observed in cycle 4 in group that switched from FIL to TBO vs TBO-only group.* Incidence of FN (temp > 38.5°C for ≥ 1 h + ANC <0.5 x 10^9/L on same day) after cycle 1 (TBO vs FIL): 15.0% vs 8.8% (P = 0.2347). *Lower overall incidence, but with a similar incidence in group that switched from FIL to TBO vs TBO-only group in cycle 4.* Mean ANC nadir [10^9/L] cycle 1 (TBO vs FIL): 2.1 vs 2.9 (no P-values reported); *similar result for cycle 4, post-switch* Mean time to ANC recovery after cycle 1 (TBO vs FIL): 6.3 days vs 4.5 days (no P-values reported); *similar result for cycle 4, post-switch* ***Safety*** **(selected drug-related TEAE during cycle 1)** • Bone pain (%, TBO vs FIL): 1.3% vs 2.5% • Myalgia (%, TBO vs FIL): 1.3% vs 1.3% • Bain pain (%, TBO vs FIL): 1.3% vs 2.5% • MSK pain (%, TBO vs FIL): 0.6% vs 0% • Pyrexia (%, TBO vs FIL): 1.9% vs 1.3% • Fatigue (%, TBO vs FIL): 0.6% vs 1.3% • GI disorders (eg, abdominal pain, nausea, or vomiting) [%, TBO vs FIL]: 2.5% vs 0% • Headache: 1.9% vs 1.3% • Blood or lymphatic system disorder (eg, thrombocythemia, thrombocytopenia) [%, TBO vs FIL): 1.3% vs 0%

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
			Overall TEAE: 94.1% with AE, 40.1% considered severe; 30.4% with serious AE, and 13.1% d/c study due to AE. 9.3% of patients died, but all deaths were considered unrelated to study drug. One patient in TBO-FIL group died of afebrile sepsis, no other deaths were due to infection/FN.
Filgrastim vs tbo-filgrastim for mobilization of PBSC for auto-HCT			
Bhamidipati et al 2017[62] Phase 2, single-center, noninferiority, ROLCT	Adults (≥ 18 years) with MM or NHL with normal bone marrow reserve eligible for auto-HCT and without receipt of a prior apheresis to collect cells for transplant • 86% of patients with MM and 11% with NHL Target collection goal of 5.0 x 10^6 CD34+ cells/kg	FIL (n = 51) vs TBO-FIL (n = 49), but only the 46 that completed transplant were in the analysis Both: 10 mcg/kg/d subQ x 5 d (from day 1 to 5) Both arms also received plerixafor 0.24 mg/kg subQ on day 4	***Efficacy*** *Primary endpoint* Mean count (x 10^6) ± SD of CD34+/kg collected on day 5 (TBO vs FIL): 11.6 ± 6.7 cells/kg vs 10.0 ± 6.8 cells/kg (P = 0.873); NI margin was "a 12% difference", but a difference was not reported. Authors considered TBO not-inferior to FIL. Majority of patients in both arms has sufficient collection with 1 apheresis procedure (79% vs 76%, P = 0.624) *Secondary endpoints* (TBO vs FIL) % with total CD34+ cells/kg collected > 5.0 x 10^6: 96% vs 96% (P = 0.916) Peripheral blood CD34+ (cells/µL) mobilization on day 5 before apheresis: 109.7 vs 92.1 (P =0.158) Transplant-related outcomes (assessed after auto-HCT): 1. *Median time to neutrophil engraftment:* 11 vs 11 days (P=0.309) 2. *Median time to platelet engraftment:* 18 vs 18 days (P=0.773) 3. *Readmission rate:* 25% vs 18% (P=0.408) Engraftment was considered a success in all patients completing auto-HCT ***Safety* (%, TBO vs FIL)** • Grade 3 or higher AE: 41% vs 33% (P=0.417) • Serious AE: 4% vs 6% (P=0.733) • Bone pain: 41% vs 43% (P=0.855) • Anemia: 28% vs 35% (P=0.458) • Thrombocytopenia: 39% vs 39% (P=0.993) • Leukocytosis (WBC count >75,000): 17% vs 20% (P=0.779) • Increased ALP: 22% vs 24% (P=0.779)

Table 3. Summary of Select Randomized Trials Identified from Search and/or Included in Systemic Reviews

First author, year, study design	Population	Treatment Comparison (n)	Results
			Most common AE: bone pain, thrombocytopenia, anemia, elevated ALP, nausea/vomiting (21% overall) 3 deaths during follow-up (not during mobilization), considered related to underlying malignancy and not drug-related

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; auto-HCT, autologous hematopoietic stem cell transplant; C, breast cancer; CHASE(R), cyclophosphamide, doxorubicin, vincristine, prednisolone ± rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CIN, chemotherapy-induced neutropenia; d, days; DD, doxorubicin and docetaxel; HL, Hodgkin's lymphoma; IE, chemotherapy regimen including etoposide and isofosfamide; L, liter; Kg, kilograms; mcg, micrograms; MM, multiple myeloma; n, number of participants randomized to intervention; NHL, non-Hodgkin's lymphoma; NI, noninferiority; PB, peripheral blood; PBSC, peripheral blood stem cells; PP, primary prophylaxis; R, rituximab; RDBCT, randomized, double-blind, controlled trial; ROLCT, randomized, open-label, controlled trial; RSBCT, randomized, single-blind, controlled trial; SD, standard deviation; SP, secondary prophylaxis; SRMA, systematic review and direct meta-analysis; SubQ, subcutaneous; TEAE, treatment-emergent adverse event; TBO or TBO-FIL, tbo-filgrastim (Granix); V_3DC, chemotherapy regimen containing vincristine, doxorubicin, and cyclophosphamide; WBC, white blood cell

[a] Only RCTs that used US-available products and at a dose recommended in prescribing information are summarized in this table
[b] Only RCTs that were not included in a SR/SRMA are included in this table (see summary in SR table for details from other trials)

Two SRs included the same RCT of sargramostim versus a G-CSF. Two additional RCTs of sargramostim were identified from old narrative reviews (not included). Below is a summary of the 3 randomized trials compared ***filgrastim and sargramostim:***

1. **Beveridge et al 1997** performed randomized double-blind trial comparing filgrastim 7 mg/kg/day (n=62) to sargramostim 193 mg/m^2/day‡‡‡‡ (n=75), both given subcutaneously by a trained patient, *for either prophylaxi*s (82% of cases) starting 1-2 days after myelosuppressive chemotherapy *or as treatment* for an absolute neutrophil count (ANC) <500/µL (18% of cases).[67] Included patients were adults (≥ 18 years old) with any malignancy that received cytotoxic chemotherapy and had not yet received a CSF. Mean age of enrolled patients was about 52 years old; breast cancer was the most common malignancy, but solid and non-solid tumors [eg, multiple myeloma] were included. The primary purpose of the study was to evaluate the relative *tolerability* of these regimens. Overall, both regimens exhibited similar tolerability. The only significant difference was a higher proportion of mild fever in the sargramostim compared to filgrastim arm (48% vs 26%, P=0.01). Otherwise there was a relatively similar incidence of local adverse events (AE), and reported systemic events, including join pain, chills, nausea, vomiting, dyspnea and headache between treatment groups. Bone pain was reported in 14% of sargramostim-treated patients compared to 12% of filgrastim-treated patients; the incidence mild bone pain

‡‡‡‡ Listed doses are as stated, but we wonder if the authors meant micrograms instead of milligrams. The recommended dose of filgrastim for prophylaxis is 5 mcg/kg/day and sagramostim is usually given at a dose of 250 mcg/m^2/day.

numerically favored filgrastim (4% vs 9%). Most AE were of mild-moderate severity, and no drug-discontinuations due to AE nor grade 4 (most severe) events occurred in either group. The study was not designed to assess efficacy, but reported a relatively similar length of hospitalization (4.6 days vs 4 days) and duration of intravenous antibiotics (4.4 days vs 6 days) for sargramostim versus filgrastim, respectively. The total duration of treatment was 7.9 days for sargramostim compared to 6.9 days for filgrastim. The study authors concluded that filgrastim and sargramostim are similarly tolerated at the studied doses, primarily among ambulatory patients that self-administered these therapies.[67]

2. **Beveridge et al 1998** conducted a randomized, double-blind multi-center trial comparing sargramostim 250 mcg/m^2/day (n=79) to filgrastim 5 mcg/kg/day (n=102), both patient-administered subcutaneously, for a mean length of 5.7 days for sargramostim versus 4.6 days for filgrastim (P=0.001 for duration comparison).[67] Included patients were adults with a malignancy experiencing an ANC <500/µL and were afebrile; patients with BMT-associated neutropenia or neutropenia associated with high-dose cyclophosphamide or cytarabine were excluded, among other exclusionary criteria. Most patients (87%) had not received CSFs previously. Comparison of the primary efficacy outcome demonstrated that patients receiving filgrastim reached an ANC of 1500/µL by an average of about 1 day faster than sargramostim-treated patients (4.6 ± 0.14 vs 5.7 ± 0.23 days, P = 0.0001). The difference in length of treatment between groups is likely due to the shorter time to reach the primary outcome with filgrastim. The time to reaching an ANC of 500/ µL was similar between groups. The proportion of patients hospitalized for neutropenic fever/IV antibiotic requirement did not significantly differ between groups (6.3% with sargramostim vs 7.8% with filgrastim, P =0.46). Duration of fever was numerically longer with filgrastim (3.6 ± 0.92 days) compared to sargramostim (1.6 ± 0.60 days, but this was not significant (P =0.14). The investigators considered the treatments to be similarly tolerated; mild chills and grade 2 fever were drug-related AE reported at a similar rate in both study arms.[67] A limitation of this study is that the outcomes of patients dropping out of the study (6 for AE; 4 due to bone pain with filgrastim and 1 due to chest pain with sargramostim), switching treatments (2 to sargramostim from filgrastim due to bone pain and 1 to filgrastim due to lack of efficacy), or lost to follow-up (2 in the filgrastim group) were not included in the analysis. The authors concluded that there was similar efficacy and tolerability between sargramostim and filgrastim in this setting, they found the 1 day difference favoring filgrastim for the primary outcome to lack clinical significance.[67]
3. In the setting of autologous transplant, **Weaver et al 2000** conducted a randomized, open-label, multicenter trial comparing filgrastim 6 mcg/kg/day (n=51) to sargramostim 250 mcg/m^2/day (n=52, both administered subcutaneously starting the day after myelosuppressive chemotherapy given for mobilization, and continued until collection of PBSCs.[68] Sargramostim for 5 days followed by filgrastim until PBSC collection was a third study arm (n=53). Included patients were adults less than 66 years old without a prior mobilization procedure with a breast, lymphoma, or multiple myeloma malignancy who would be treated with high-dose chemotherapy requiring PBSC support. One day after the PBSC infusion, all patients did receive filgrastim 6 mcg/kg/day until neutrophil recovery and patients had access to other supportive care treatments (eg, prophylactic antibiotic). Patients treated with filgrastim mobilized a significantly higher median number of CD34+ cells than sargramostim alone, 12 vs 5.4 x 10^6/kg, P = 0.0001). Per authors, the optimal target was considered to be 5 x 10^6 cells/kg, so both groups reached that but the sargramostim group required a higher median number of

apheresis procedures (3 vs 2, P =0.002) and a longer median treatment duration (14 vs 12 days, P =0.0001) to reach the target. The chemotherapy mobilization regimen used (2 possible options) also influenced the number of cells mobilized; sargramostim and filgrastim were similarly effective in reaching the target with one of the chemo-mobilization regimens, but not the other. Regarding differences in toxicities after the mobilization chemotherapy, ANC recovery was faster in the filgrastim group than sargramostim, and treatment with filgrastim was also significantly better in terms of fewer required red blood cell transfusion, lower occurrence of fever, and fewer hospital admissions. The third sequential treatment arm was found to be similar to filgrastim alone, and more effective than sargramostim alone.[68] The relative tolerability/toxicity of the CSF regimens was not clearly addressed in the publication. The investigators concluded filgrastim was superior to sargramostim for mobilization of hematopoietic stem cells.[68]

Appendix H: Detailed Comparison of Warnings and Precautions

Table 1. Detailed Warnings and Precautions for Colony Stimulating Factors from Prescribing Information

filgrastim (Neupogen)[3] and biosimilars (Nivestym, Zarxio, Releuko)	tbo-filgrastim (Granix)[13]	pegfilgrastim (Neulasta)[14] and biosimilars (Fulphila, Udenyca, Ziextenzo, Nyvepria)[15-18]	Sargramostim (Leukine)[4]
Warnings and Precautions			
Serious allergic reactions: serious hypersensitivity reactions, including anaphylaxis, have occurred during use of filgrastim and pegfilgrastim products; usually during the first treatment. Treat the allergic reaction, and stop treatment of the (peg)filgrastim product if such a reaction occurs, and do not reinitiate.			**Hypersensitivity reactions:** serious reactions including anaphylaxis have occurred. Stop treatment if such a reaction occurs, and do not reinitiate.
Capillary leak syndrome: Events, including possible life-threatening cases due to treatment delays, have occurred after use of (peg)filgrastim products; common symptoms of CLS include hypotension, hypoalbuminuria, edema, and hemoconcentration. Monitor and treat CLS with standard treatment.			**Effusions (pleural/pericardial) and capillary leak syndrome:** Fluid retention has occurred; CLS estimated to occur in <1% of patients. *Use cautiously in patients where fluid retention is a concern (eg, heart failure, existing effusions).* Monitor body weight/hydration during treatment.
Leukocytosis: Filgrastim products: *Patients receiving myelosuppressive chemo:* At doses >5 mcg/kg/day, 2% of patients experienced WBC >100,000/mm^3. Monitor CBC at least twice weekly. D/c filgrastim products if ANC >10,000/mm^3 post nadir to minimize risks and in light of limited benefit. *PBPC collection/treatment:* D/c (peg)filgrastim products if leukocytes >100,000/mm^3 Pegfilgrastim products: High WBC counts (>100 x 10^9/L) have occurred. Monitor CBC during treatment.			**Leukocytosis:** WBC ≥ 50,000/mm^3 observed. Monitor CBC with differential twice weekly during treatment, and consider dose adjustments as clinically indicated.
Potential growth effect on malignant cells: cannot exclude possible growth factor effects for any tumors; safe use for CML and myelodysplasia is not established. When used for PBPC mobilization, it is possible tumor cells could also be collected by leukapheresis.			**Potential growth effect on malignant cells:** cannot exclude growth factor effects, especially for myeloid malignancies. D/c this treatment if malignant disease progression occurs.

Table 1. Detailed Warnings and Precautions for Colony Stimulating Factors from Prescribing Information

filgrastim (Neupogen)[3] and biosimilars (Nivestym, Zarxio, Releuko)	tbo-filgrastim (Granix)[13]	pegfilgrastim (Neulasta)[14] and biosimilars (Fulphila, Udenyca, Ziextenzo, Nyvepria)[15-18]	Sargramostim (Leukine)[4]
Not recommended for simultaneous administration with chemo or radiation: Filgrastim products are not recommended for use within 24 hours before or after cytotoxic chemo. Use has not been evaluated during concurrent radiation.			**Not recommended for administration within 24 hours of chemo or radiation:** owing to effects on hematopoietic progenitor cells; higher grade AE and higher mortality rates have been observed when used in that time frame.
Potentially fatal splenic rupture: Cases have occurred after use of filgrastim and pegfilgrastim products. Evaluate patients with possible splenic enlargement or rupture symptoms, and d/c treatment if suspected/confirmed (per Granix labeling).			**Infusion-related reactions (eg, respiratory distress, hypoxia hypotension):** may occur with first dose in a cycle; watch for these symptoms, and reduce infusion rate as indicated.
Acute respiratory distress syndrome (ARDS): Cases have occurred after use of filgrastim and pegfilgrastim products. Evaluate for ARDS in patients with fever and lung infiltrates or respiratory impairment, and d/c treatment if ARDs occurs.			**Supraventricular arrythmias:** reversible events have been reported, especially in patients with a history of arrythmia. *Use cautiously in patients with cardiac disease.*
Severe sickle cell crises in people with sickle cell disorders (SCD): Crises, including death, have occurred in SCD patients during use of filgrastim and pegfilgrastim products. Treatment should be stopped if a crises occurs.			**Immunogenicity:** anti-drug antibodies have developed, especially with longer use. Use for the minimum needed duration.
Glomerular nephritis: Usually reversible cases (characterized by azotemia, hematuria, proteinuria and confirmed by renal biopsy) have occurred during use of filgrastim and pegfilgrastim products. If the (peg)filgrastim product is considered a likely cause, consider holding treatment or reducing the dose.			**Risk of serious adverse reactions, including fatalities, to benzoyl alcohol (infants):** avoid formulations containing benzoyl alcohol in neonates or low birth weight infants.
Thrombocytopenia: Events have occurred during use of filgrastim products. Patient's platelet counts should be monitored during therapy.		**Thrombocytopenia:** Events have occurred during use of pegfilgrastim products. Patient's platelet counts should be monitored during therapy.	
Aortitis: Events, starting as early as 1 week of treatment, have occurred during use of filgrastim and pegfilgrastim products. Evaluate aortitis as a potential cause in patients with suspect signs/symptoms without a known cause. D/c treatment if it is suspected.			

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filgrastim (Neupogen)[3] and biosimilars (Nivestym, Zarxio, Releuko)	tbo-filgrastim (Granix)[13]	pegfilgrastim (Neulasta)[14] and biosimilars (Fulphila, Udenyca, Ziextenzo, Nyvepria)[15-18]	Sargramostim (Leukine)[4]
Nuclear imaging: Transient bone-imaging changes are expected due to response in the bone marrow of patients treated with filgrastim and pegfilgrastim products; consider this for imaging result interpretation.			
MDS and AML in patients with breast/lung cancer, and severe chronic neutropenia (SCN): ▪ *Breast/lung cancer:* MDS/AML is associated with use of filgrastim products combined with chemo/radiation. ▪ *SCN:* Available data suggests that development of MDS/AML in filgrastim product recipients is associated with congenital neutropenia specifically. The effect of these products on abnormal cytogenetics/MDS/AML is not known; these events have also occurred in untreated patients with congenital neutropenia. Consider treatment risks: benefits if abnormalities occur in SCN patients. Monitor for signs/symptoms of MDS/AML.		**MDS and AML in patients with breast/lung cancer:** MDS/AML is associated with use of pegfilgrastim products combined with chemo/radiation in breast/lung cancer patients. Monitor for signs/symptoms of MDS/AML.	
Alveolar hemorrhage and hemoptysis in healthy PBPC donors during mobilization (not an approved population for use): Events that required hospitalization have occurred that were reversible upon discontinuation of treatment.		**OBI device only (Neulasta) - allergies to acrylics:** The device uses an acrylic adhesive, which may cause a reaction in patients sensitive to it.	

Table 1. Detailed Warnings and Precautions for Colony Stimulating Factors from Prescribing Information

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Cutaneous vasculitis: Events (mostly moderate to severe, and in SCN patients during chronic treatment) have occurred. Hold filgrastim product; may restart at lower dose upon resolution.		**OBI device only (Neulasta) - potential for device failure:** Results in a missed or partial dose; patients should contact their care provider if this occurs.	

Shading: Green shading = similar warning across 3+ product groups including G-CSF and GM-CSF; Red shading = similar warning for all G-CSF products; Yellow shading = warning unique to a single product/product group (eg, filgrastim and its biosimilars); Blue shading = similar warning for filgrastim-related products, but not pegfilgrastim products.

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; AE, adverse events; CLS, capillary leak syndrome; CML, chronic myeloid leukemia; D/c, discontinue; G-CSFs, granulocyte colony-stimulating factors; GM-CSFs, granulocyte macrophage colony-stimulating factors (eg, sargramostim); MDS, myelodysplastic syndromes; OBI, on-body implant (refers to the Neulasta OnPro kit); PBPC, peripheral blood progenitor cell; SCN, severe chronic neutropenia