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Drug Class Update with New Drug Evaluation: Colony Stimulating Factors

Date of Review: October 2023

Generic Name: eflapegrastim

Date of Last Review: October 2022
Dates of Literature Search: 06/09/2022 – 07/11/2023
Brand Name (Manufacturer): Rolvedon™
Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Evaluate any new comparative evidence for the granulocyte colony stimulating factors (G-CSFs) and granulocyte-macrophage colony stimulating factors (GM-CSFs) since the last Pharmacy and Therapeutics (P & T) Committee review in 2022. Review safety and efficacy data for eflapegrastim, a new long-acting G-CSF.

Plain Language Summary:
- This review evaluates a new medicine, eflapegrastim, used to prevent neutropenia (a low white blood cell count), which can happen after receiving treatment for cancer with chemotherapy. Chemotherapy kills cancer cells as well as healthy white blood cells. A low number of white blood cells decreases the body's ability to fight infections. If someone with neutropenia also develops a fever, it is called febrile neutropenia, and it is life-threatening.
- Medicines known as granulocyte colony-stimulating factors help the body make white blood cells. These medicines are used to prevent complications from low white blood cell counts, such as infection or fever, when people receive some types of chemotherapy.
- The United States Food and Drug Administration has approved 3 granulocyte colony-stimulating factors: filgrastim, pegfilgrastim, and eflapegrastim. All 3 of these medicines are given by an injection that is administered by a doctor or nurse. Some people can be taught how to give these medicines to themselves at home.
- Eflapegrastim was approved in September 2022. In 2 clinical trials, eflapegrastim was compared to pegfilgrastim, a commonly used granulocyte colony-stimulating factor, in adults with early-stage breast cancer who received chemotherapy. There were no differences between eflapegrastim and pegfilgrastim in the number of days these patients had low white blood cell counts.
- Eflapegrastim can cause low blood platelet counts, which can lead to an increased chance of bleeding. If people who receive eflapegrastim notice unusual bruising or bleeding, they should contact their doctor right away. Eflapegrastim can also make people feel tired, have diarrhea, nausea, headache, bone pain, back pain or rash.
- Providers must explain to the Oregon Health Authority why someone needs eflapegrastim before Medicaid will pay for it. This process is called prior authorization.

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Research Questions:

1. Is there any new comparative evidence for G-CSF treatments for important outcomes such as mortality, infection or hospitalizations?
2. Is there any new comparative evidence based on the harm outcomes (i.e., bone pain, nausea, therapy-related myeloid neoplasms) for G-CSF treatments?
3. Are there subpopulations based on race, ethnicity, age, gender, or socioeconomic status for which specific G-CSF therapies may be more effective or associated with less harm?
4. What is the evidence of efficacy and harms for the new G-CSF treatment, eflapegrastim, in preventing febrile neutropenia?

Conclusions:

- No new high-quality comparative evidence for the safety and efficacy of G-CSF treatments has been published since the last class review in October 2022.
- In September 2022, the FDA approved pegfilgrastim-fpgk (STIMUFEND®), a new biosimilar formulation of pegfilgrastim. This medication is indicated to reduce the incidence of febrile neutropenia in patients with cancer receiving myelosuppressive chemotherapy.[1]
- The pegfilgrastim biosimilar, pegfilgrastim-cbqv (UDENYCA®), received an expanded indication to increase survival in patients exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome) in November 2022.[2]
- Pegfilgrastim-fpgk injection and pegfilgrastim-cbqv are not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantion.[1,2]
- No subpopulations based on race, ethnicity, age, gender, or socioeconomic status were identified for which specific G-CSF therapies may be more effective or associated with less harm.
- The FDA approved the long-acting G-CSF eflapegrastim-xnst (ROVLEDON™) for subcutaneous injection in September 2022.[3] Eflapegrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adults patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with clinically significant incidence of febrile neutropenia.[3]
- Efficacy of eflapegrastim was evaluated in 2 randomized, open-label, active-controlled, non-inferiority clinical trials ADVANCE[4] and RECOVER.[5] In each study, a fixed dose of eflapegrastim 13.2 mg or pegfilgrastim 6 mg was administered subcutaneously on day 2 of each chemotherapy cycle, 24 hours after the last dose of chemotherapy.[4,5] The primary non-inferiority efficacy endpoint was the duration of severe neutropenia in cycle 1, defined as the number of days of severe neutropenia (absolute neutrophil count [ANC] < 0.5×10^9 per L) from the day of first occurrence of an ANC below that threshold.[4,5]
- In the ADVANCE trial, the mean Cycle 1 duration of severe neutropenia was 0.20 ± 0.503 days for the eflapegrastim arm versus 0.35 ± 0.683 days for the pegfilgrastim arm.[4] The difference in duration of severe neutropenia between the eflapegrastim treatment arm and the pegfilgrastim treatment arm was -0.148 days (95% CI -0.265 to -0.033 days; p<0.0001; low-quality evidence).[4] In the RECOVER trial, the difference in duration of severe neutropenia between the eflapegrastim treatment arm and the pegfilgrastim treatment arm was -0.074 days (95% CI, -0.292 to 0.129; p<0.0001; low-quality evidence).[5] Non-inferiority to pegfilgrastim was demonstrated for eflapegrastim (upper bound of 95% CI <0.62 days) in both trials.[6]
- The most common adverse reactions (≥ 20%) for eflapegrastim treatment arms were fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia and back pain.[3]

Recommendations:

- No PDL recommendations based on clinical evidence.
- After review of medication costs in the executive session, NYVEPRIA (pegfilgrastim-apgf) was made non-preferred on the PDL.

Summary of Prior Reviews and Current Policy

- Evidence for the colony stimulating factors was last evaluated in October 2022. There are no class specific prior authorization criteria beyond preferred and non-preferred status. Preferred products include the G-CSFs; filgrastim and pegfilgrastim, and the GM-CSF, sargramostim. Non-preferred products billed through the pharmacy are required to meet nonspecific prior authorization criteria which requires validation of an FDA approved indication and funding level. The preferred drug list status for each colony stimulating factor is presented in **Appendix 1**.
- Previous evidence summaries concluded there were no compelling differences in efficacy or harms between G-CSF products.[7] G-CSF products are recommended for prophylaxis of febrile neutropenia, treatment of febrile neutropenia, and for mobilization of progenitor cells in cell transplant.[7] Evidence is generally of moderate quality for these indications.
- Guidelines from the National Comprehensive Cancer Network (NCCN) continue to recommend G-CSFs for prophylaxis of febrile neutropenia, treatment of febrile neutropenia, and for mobilization of progenitor cells in cell transplant.[8] The United States (U.S.) Food and Drug Administration (FDA) labeled indications vary by product and are summarized in **Appendix 5**.
- The number of patients with claims (pharmacy or medical) for G-CSF products is relatively small in the fee-for-service (FFS) population and most products are billed through medical claims where the preferred drug list (PDL) does not apply. Since 2021, utilization has shifted from use of originator products to almost exclusively biosimilar products.

Background:

Treatment with myelosuppressive chemotherapy puts patients at risk of developing neutropenia.[9] The risk of febrile neutropenia and life-threatening infections increases in patients with a low ANC. Neutropenia is usually defined as an ANC less than 1500 or 1000 cells/microL; severe neutropenia as an ANC less than 500 cells/microL or an ANC that is expected to decrease to less than 500 cells/microL over the next 48 hours; and profound neutropenia as an ANC less than 100 cells/microL.[10] Mortality rates in patients who are hospitalized for febrile neutropenia are around 10%, and increase to above 20% for patients with multiple and/or severe co-morbidities.[11] The duration and severity of neutropenia are major risk factors for the development of febrile neutropenia and for life-threatening infection in patients receiving chemotherapy.[9] In patients with febrile neutropenia, dose reductions or treatment delays can occur, which may compromise treatment outcomes.[9] Granulocyte colony-stimulating factors, which were first introduced for clinical use in the 1990s, reduce the incidence of neutropenia and improve patient outcomes.[9] The need for daily injections was reduced by development of the long-acting G-CSF pegfilgrastim.[9] However, G-CSF–induced bone pain, and continued vulnerability to infection in the first week after chemotherapy remain unmet medical needs.[9]

The 2023 NCCN clinical guidelines for prevention and management of chemotherapy-induced neutropenia recommend the use of supportive care with G-CSFs (i.e., filgrastim, Tbo-filgrastim, pegfilgrastim) in patients with solid tumors and non-myeloid malignancies with intermediate (10% to 20%) and high (>20%) risk factors which are based on the disease, chemotherapy regimen, patient risk factors, and treatment intent (curative versus palliative).[8] The role for G-CSF in myeloid malignancies is more limited due to concern for stimulation of the myeloid compartment by the G-CSF.[9] For this reason, G-CSF administration is not recommended during induction treatment for patients with acute myeloid leukemia but can be considered during consolidation therapy.[8] However, there are limited long-term outcomes data in these cases.[9]

Inclusion criteria for the phase 3 randomized controlled trials (RCTs) for eflapegrastim utilized the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale. This scale is used by researchers when planning cancer clinical trials to study new treatments.[12] This scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.).[12] It is also a way for physicians to track changes in a patient's level of functioning as a result of treatment during the trial.[12] A description of each ECOG grade is presented in **Table 1.**

Table 1. ECOG Performance Status Scale[13]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[14-16]

New Guidelines: No new guidelines were identified for this review.

New Formulations and Indications:
New Formulation
In September 2022, the FDA approved pegfilgrastim-fpgk (STIMUFEND®), a new biosimilar formulation of pegfilgrastim.[1] Pegfilgrastim-fpgk is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1] The approved dose is 6 mg administered subcutaneously once per chemotherapy cycle.[1] Pegfilgrastim-fpgk injection is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantion.[1]

New Indication

In November 2022, the FDA approved an expanded indication for pegfilgrastim-cbqv (UDENYCA®) to increase survival in patient exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).[2] Efficacy studies of pegfilgrastim-cbqv could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons.[2] Approval of this indication was based on efficacy studies conducted in animals and data supporting pegfilgrastim's effect on severe neutropenia in cancer patients receiving myelosuppressive chemotherapy.[2] The dosing for this indication is 6 mg administered subcutaneously one week apart for 2 doses.[2] The first dose should be administered as soon as possible after a suspected or confirmed exposure to myelosuppressive doses of radiation.[2] For pediatric patients weighing less than 45 kg, the manufacturer recommends weight based dosing according to a protocol provided in the prescribing information.[2] Prior to this approval, pegfilgrastim-cbqv was indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignances receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[2] Pegfilgrastim-cbqv is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantion.[2]

New Safety Alerts:

Table 1. Description of New FDA Safety Alerts[17]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Pegfilgrastim-jmdb and Pegfilgrastim-bmez	FULPHIA and ZIEXTENZO	3/2021	Warnings and Precautions	**Thrombocytopenia** Thrombocytopenia has been reported in patients receiving pegfilgrastim. Monitor platelet counts. **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer** MDS and AML have been associated with the use of pegfilgrastim in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.
Pegfilgrastim-apgf	NYVEPRIA	4/2021	Warnings and Precautions	**Thrombocytopenia** Thrombocytopenia has been reported in patients receiving pegfilgrastim. Monitor platelet counts. **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer** MDS and AML have been associated with the use of pegfilgrastim in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer.

				Monitor patients for signs and symptoms of MDS/AML in these settings.
Pegfilgrastim-cbqv	UDENYCA	6/2021	Warnings and Precautions	**Thrombocytopenia** Thrombocytopenia has been reported in patients receiving pegfilgrastim. Monitor platelet counts. **Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer** MDS and AML have been associated with the use of pegfilgrastim in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.
Filgrastim-sndz	ZARXIO	7/2021	Warnings and Precautions	**Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)** Patients with Breast and Lung Cancer: MDS and AML have been associated with the use of filgrastim products in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.

Randomized Controlled Trials:
A total of 77 citations were manually reviewed from the initial literature search. After further review, 77 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Eflapegrastim-xnst (ROVLEDON™)
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

The FDA approved the long-acting G-CSF eflapegrastim-xnst (ROVLEDON™) for subcutaneous injection in September 2022.[3] Eflapegrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adults patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with clinically significant incidence of febrile neutropenia.[3] This medication consists of a recombinant human G-CSF analog conjugated to a human aglycosylated immunoglobulin (Ig) G4 Fc fragment with a short polyethylene glycol linker.[4] The addition of an Fc fragment and the large size of the molecule extends the drug half-life by decreasing clearance, and there is increased uptake in the bone marrow, possibly due to the interaction of the Fc fragment with receptors on surface of endothelial cells.[4] Similar to pegfilgrastim, eflapegrastim has not been evaluated in patients undergoing stem cell

mobilization.[6] Therefore, eflapegrastim is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.[3] The recommended eflapegrastim dose is 13.2 mg administered subcutaneously by a healthcare professional once per chemotherapy cycle, 24 hours after completion of cytotoxic chemotherapy.[3]

Clinical Efficacy:
Efficacy of eflapegrastim was evaluated in 2 randomized, open-label, active-controlled, non-inferiority clinical trials of similar design called ADVANCE[4] and RECOVER.[5] The trials enrolled a total of 643 patients with early-stage breast cancer who received 4 cycles of docetaxel (**T**AXOTERE) with **c**yclophosphamide (TC) as the chemotherapy regimen.[4,5] Docetaxel and cyclophosphamide (TC) chemotherapy is considered a standard regimen for adjuvant therapy for node-negative or low-risk node-positive breast cancer.[6] However, according to the NCCN guidelines, the TC regimen is associated with high risk for febrile neutropenia (>20%) which necessitates the use of a G-CSF.[6] In each study, a fixed dose of eflapegrastim 13.2 mg or pegfilgrastim 6 mg was administered subcutaneously on day 2 of each chemotherapy cycle, 24 hours after the last dose of chemotherapy.[4,5] Dose modifications for eflapegrastim or pegfilgrastim were not permitted. The FDA approval of pegfilgrastim was based on 3 double-blind studies in patients with breast cancer, so it was an appropriate comparator for eflapegrastim in these 2 RCTs.[6] Both ADVANCE and RECOVER had identical endpoints, statistical hypotheses and methods.[6] The differences were the planned numbers of patient enrollment (ADVANCE: 400 patients, RECOVER: 218 patients) and statistical power.[6] The median age of patients enrolled in the 2 trials was 60 years (range 24 to 88 years), the majority of patients were female (> 99%), 77% were White and 12% were Black. Most of the patients (81%) were enrolled in clinical sites based in the United States.[6]

The Intent-to-Treat (ITT) Population included all patients who were randomized in each RCT.[6] Patients were analyzed in the treatment arm as randomized if the actual treatment assignments deviated from the randomization scheme.[6] The Per-Protocol (PP) Population included all patients in the ITT Population with no important protocol deviations that affected the analysis of the primary efficacy endpoint.[6] Patients were analyzed as treated if the actual treatment assignments deviated from the randomization scheme.[6] Primary efficacy analysis was based on the ITT Population.[6] Analysis based on the PP Population was performed as a sensitivity analysis.[6]

The primary non-inferiority efficacy endpoint was the duration of severe neutropenia in cycle 1, defined as the number of days of severe neutropenia (ANC < 0.5×10^9 per L) from the day of first occurrence of an ANC below that threshold.[6] The non-inferiority of eflapegrastim to pegfilgrastim would be declared if the upper bound of 95% CI of the difference in mean days of severe neutropenia between the treatment arms was less than 0.62 days.[6] The FDA recommended that a 0.62 day non-inferiority margin should be used in order to maintain the results of the randomized trials comparing the duration of neutropenia of pegfilgrastim to filgrastim which led to the approval of pegfilgrastim.[6] Blood samples for complete blood counts (CBCs) with differential were collected pretreatment and on day 1 and daily on days 4–15 of cycle 1 and on days 1, 4, 7, and 15 in subsequent cycles.[4] However, if an ANC equal to or less than 1.0×10^9/L was reported at any time in cycles 2 through 4, daily CBCs were performed until the ANC recovered to 1.5×10^9 per Liter or greater.[4] All blood analyses were performed by an independent central laboratory.[4]

In addition to duration of severe neutropenia in cycles 2 through 4, other secondary endpoints assessed in each cycle included time-to-ANC recovery (time-from-chemotherapy administration to ANC ≥1.5×10^9 per Liter after the expected nadir), depth of ANC nadir (lowest ANC value), incidence of febrile neutropenia (ANC <1.0×10^9 per L and either temperature >38.3°C or two consecutive readings ≥38.0°C over 2 hours); incidence of neutropenic complications (anti-infective use and/or hospitalizations); and safety (overall adverse event [AE] rates; AEs of special interest: musculoskeletal-related, splenic rupture, leukocytosis, and anaphylaxis).[4] Although a hierarchical closed testing procedure was planned for the key secondary efficacy endpoints, no clear statistical hypotheses were pre-

specified and stated in the statistical analysis plan.[6] According to the FDA reviewers, because the studies were not powered to test non-inferiority for any of the key secondary endpoints, failing on the superiority tests would not lead to any labeling claim.[6]

In the ADVANCE trial, the mean Cycle 1 duration of severe neutropenia was 0.20 ± 0.503 days for the eflapegrastim arm versus 0.35 ± 0.683 days for the pegfilgrastim arm.[4] The difference in duration of severe neutropenia between the eflapegrastim treatment arm and the pegfilgrastim treatment arm was -0.148 days (95% CI -0.265 to -0.033 days; p<0.0001).[6] This met the study's primary endpoint of eflapegrastim non-inferiority to pegfilgrastim (upper bound of 95% CI < 0.62 days).[4] The incidence of severe neutropenia (Grade 4, $<0.5 \times 10^9$/L) in cycle 1 was 15.8% (n=31) for the eflapegrastim arm compared with 24.3% (n= 51) for the pegfilgrastim arm, resulting in an 8.5% absolute risk reduction (95% CI -16.1 to -0.2; p=0.034) for eflapegrastim versus pegfilgrastim.[4] In the RECOVER trial, the mean Cycle 1 duration of severe neutropenia was 0.31 ±0.69 days for the eflapegrastim arm versus 0.39 ±0.95 days for the pegfilgrastim arm.[5] The difference in duration of severe neutropenia between the eflapegrastim treatment arm and the pegfilgrastim treatment arm was -0.074 days (95% CI, -0.292 to 0.129; p<0.0001).[5] Non-inferiority to pegfilgrastim was demonstrated for the eflapegrastim treatment arm (upper bound of 95% CI <0.62 days).[6]

Both studies individually met the non-inferiority criteria for the primary endpoint of duration of severe neutropenia in Cycle 1 in the ITT population.[6] The results in the Per Protocol population and additional sensitivity analyses were consistent with the results in the ITT population.[6] There were no outliers in the subgroup analyses of duration of severe neutropenia in Cycle 1 by age, gender, race, disease status, region, and body weight in both studies.[6] The analyses of all secondary efficacy endpoints including time to ANC recovery, depth of ANC nadir, and incidence of febrile neutropenia also showed that there were no significant differences between eflapegrastim and pegfilgrastim.[6] Additional study details are presented in the comparative evidence table (**Table 4**).

Study Limitations:
Both trials were open-label, non-inferiority assessments, which is lower quality evidence compared with blinded RCTs designed to demonstrate superiority of one agent over another. The enrollment in both trials lacked diversity, as the majority of enrolled patients were White. Safety and efficacy of eflapegrastim are not established in pediatric patients, although a trial is currently being conducted in this population.[6] In contrast, both pegfilgrastim and filgrastim are FDA-approved for use in pediatrics.[18] Given the marginal benefits of eflapegrastim compared with pegfilgrastim, selection of a preferred agent may be based on a cost comparison of both agents.

Clinical Safety:
The safety review of eflapegrastim was primarily based on a total of 640 patients (eflapegrastim: 314 patients, pegfilgrastim: 326 patients) who participated in the two phase 3 trials.[3] The most common adverse reactions (≥ 20%) for eflapegrastim treatment arms were fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia and back pain.[6] The overall incidence of serious adverse reactions (SAEs) was similar in the two arms (eflapegrastim: 2%, pegfilgrastim: 3%). The most frequently reported SAEs observed in more than 2 patients in the eflapegrastim arm were pyrexia, sepsis, febrile neutropenia, diarrhea and chest pain; and the incidences of these SAEs were similar to those observed in the pegfilgrastim arm.[6] Permanent discontinuation due to an AE occurred in 4% of patients who received eflapegrastim.[3] Rash was the adverse reaction requiring permanent discontinuation in 3 patients who received eflapegrastim.[3] A complete summary of common AEs occurring in more than 10% of study participants in the 2 RCTs is presented in **Table 2**.

Table 2. Common Adverse Reactions Observed In Clinical Trials With Eflapegrastim Compared To Pegfilgrastim.[3]

Adverse Effect	Eflapegrastim (n=314) N (%)	Pegfilgrastim (n=326) N (%)
Fatigue	181 (58%)	192 (59%)
Nausea	162 (52%)	166 (51%)
Diarrhea	125 (40%)	126 (39%)
Bone Pain	119 (38%)	121 (37%)
Headache	92 (29%)	90 (28%)
Pyrexia	87 (28%)	84(26%)
Anemia	77 (25%)	52 (16%)
Rash	77 (25%)	99 (30%)
Myalgia	69 (22%)	49 (15%)
Arthralgia	66 (21%)	48 (15%)
Back Pain	63 (20%)	55 (17%)
Decreased Appetite	61 (19%)	50 (15%)
Peripheral Edema	57 (18%)	53 (16%)
Abdominal Pain	53 (17%)	67 (21%)
Dizziness	50 (16%)	38 (12%)
Dyspnea	49 (16%)	44 (13%)
Cough	48 (15%)	51 (16%)
Thrombocytopenia	44 (14%)	17 (5%)
Pain	37 (12%)	42 (13%)
Pain in Extremity	36 (11%)	42 (13%)
Local Administration Reactions	34 (11%)	27 (8%)
Flushing	32 (10%)	27 (8%)

Look-alike / Sound-alike Error Risk Potential: No medications have been identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Incidence of infection
2) Incidence of febrile neutropenia
3) Duration of febrile neutropenia
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Duration of severe neutropenia (ANC < 0.5 x 10^9/L) in Cycle 1 of chemotherapy

Table 3. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Eflapegrastim-xnst is a recombinant human granulocyte growth factor that binds to G-CSF receptors on myeloid progenitor cells and neutrophils, triggering signaling pathways that control cell differentiation, proliferation, migration and survival.
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd = 1.44 L; protein binding not reported.
Elimination	Not detected in urine.
Half-Life	36.4 hours
Metabolism	Eflapegrastim-xnst is expected to be metabolized by endogenous degradation following receptor-mediated internalization by cells bearing the G-CSF receptor.

Abbreviations: G-CSF = granulocyte colony-stimulating factor; L = Liters; N/A = not applicable; Vd = Volume of distribution

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.Schwartzberg, L. et al.[4] ADVANCE OL, AC, MC, NI, Phase 3 RCT	1. Eflapegrastim 13.2 mg SC on day 2 of chemotherapy cycle (24 hours post-chemotherapy) for 4 cycles of chemotherapy 2. Pegfilgrastim 6 mg SC on day 2 of chemotherapy cycle (24 hours post-chemotherapy) for 4 cycles of chemotherapy	Demographics: 1.Female: >99% 2.Median Age: 61 yo 3. Age ≥ 65 yo: 40% 4.Race -White: 78% -Black: 14% -Asian: 4% -Other 4% 5. Ethnicity Hispanic/Latino: 18% 6. ECOG performance status of 0: 71% Key Inclusion Criteria: -Age ≥ 18 y -New diagnosis of histologically confirmed early-stage breast cancer (Stage I to Stage 3A). -Candidate for chemotherapy -Adequate hematological, renal and hepatic function -ECOG performance status ≤2 Key Exclusion Criteria: -Active concurrent malignancy	ITT: 1. 196 2 .210 PP: 1. 187 2. 196 Attrition: 1.28 (14%) 2.30 (14%)	Primary Endpoint: Mean number of days of severe neutropenia (ANC < 0.5 x 10^9/L in Cycle 1 of chemotherapy in ITT population 1 .0.20 ± 0.503 days 2. 0.35 ± 0.683 days Difference: -0.148 days 95% CI -0.265 to -0.033 P<0.0001 Secondary Endpoints: Time to ANC recovery in Cycle 1 1. 3.24 days 2. 3.49 days Difference: 0.25 days; P=0.685 Median depth of ANC nadir in Cycle 1 1. 1.6 x 10^9/L 2. 1.3 x 10^9/L Difference: 0.16; P=0.16	NA NS NS	Drug-Related AEs 1. 164 (83%) 2. 146 (70%) SAEs 1. 36 (18%) 2. 29 (14%) Discontinuation due to AEs 1. 3 (5%) 2. 2 (5%) Bone Pain 1. 63 (32%) 2. 67 (32%) Arthralgia 1. 38 (19%) 2. 26 (13%) 95% CI and p-values NR	NA for all	**Risk of Bias (Low/High/Unclear)**: Selection Bias: Low. Randomized 1:1 via IWRS. Baseline characteristics balanced between groups. Open-label study design permitted patients and investigators to be aware of treatment assignment. Performance Bias: High. No blinding due to open-label study design. Detection Bias: Unclear. All blood analyses were performed by an independent central laboratory. However, investigators were aware of treatment assignment. Attrition Bias: Low. Similar attrition rates in both arms. Attrition due to AEs and patient withdrawal of consent. Reporting Bias: Low. Study protocol available at clinicaltrials.gov website. All prespecified outcomes were reported. Other Bias: Unclear. Study funded by manufacturer. None of the clinical investigators were full or part-time employees of the Sponsor for the RCT. **Applicability**: Patient: Primarily white female population with limited diversity (78% of subjects were White). Intervention: Eflapegrastim dosing determined in Phase 2 weight-based, dose-ranging study in

		- Known sensitivity to *E.Coli* derived products -Concurrent adjuvant cancer therapy -Locally recurrent/ metastatic breast cancer -Active infection -Prior bone marrow or stem cell transplant		Incidence of febrile neutropenia in Cycle 1 1. 4 (2%) 2. 2 (1%) Difference: 1%; P=0.44 -Incidence of neutropenic complications 1. 8(4.1%) 2. 8 (3.8%) Difference: 0.3% P value NR: NS	NS NS			patients (n=148) with early breast cancer and candidates for chemotherapy. Comparator: Pegfilgrastim has demonstrated efficacy in reducing duration of neutropenia in early breast cancer patients and is an appropriate active comparator for this RCT. Outcomes: Duration of severe neutropenia in first cycle of chemotherapy was the primary efficacy outcome in pegfilgrastim RCTs. Appropriate to use a similar outcome in eflapegrastim trial. Setting: 82 sites in 3 countries. Percent of enrolled patients by country: United States (97%); Canada (2%); Korea (1%)
2. Cobb WC, et al.[5] RECOVER OL, AC, MC, NI, Phase 3 RCT	1. Eflapegrastim 13.2 mg SC on day 2 of chemotherapy cycle (24 hours post-chemotherapy) for 4 cycles of chemotherapy 2. Pegfilgrastim 6 mg SC on day 2 of chemotherapy cycle (24 hours post-chemotherapy) for 4 cycles of chemotherapy	Demographics: 1.Female: 100% 2.Median Age: 59 yo 3. Age ≥ 65 y: 35% 4. Race -White: 76% -Black: 5% -Asian: 15% -Other <1% 5. Ethnicity Hispanic/Latino: 14% 6. ECOG performance status of 0: 80% Key Inclusion Criteria: see above Key Exclusion Criteria: see above	ITT: 1. 118 2. 119 PP: 1. 100 2. 111 Attrition: 1. 14 (12%) 2. 16 (13%)	Primary Endpoint: Mean number of days of severe neutropenia (ANC < 0.5 x 10^9/L in Cycle 1 of chemotherapy 1 .0.31 ± 0.688 days 2. 0.39 ± 0.949days Difference: -0.073 days 95% CI -0.292 to 0.129 P<0.0001 Secondary Endpoints: Time to ANC recovery in Cycle 1 1. 3.49 days 2. 3.35 days Difference: 0.14 days; P=0.866 Median depth of ANC nadir in Cycle 1 1. 1.60 x 10^9/L 2. 1.57x 10^9/L Difference: 0.03 x 10^9/L P=0.36 Incidence of febrile neutropenia in Cycle 1 1. 1 (0.8%) 2. 4 (3.4%) Difference: 2.6%; P=0.37	NA NS NS NS	Drug-Related AEs 1. 74 (63%) 2. 72 (61%) SAEs 1. 12 (10%) 2. 15 (16%) Discontinuation due to AEs 1. 3 (3%) 2. 3 (3%) Bone Pain 1. 40 (34%) 2. 45 (38%) Arthralgia 1. 9 (8%) 2. 3 (3%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: see above Detection Bias: see above Attrition Bias: see above Reporting Bias: see above Other Bias: Unclear. Study funded by manufacturer. 3 authors are employees of the manufacturer. **Applicability**: Patient: All female, predominantly white population with limited diversity. Intervention: see above Comparator: see above Outcomes: see above Setting: 74 sites in 6 countries. Percent of enrolled patients by country: United States (55%); Canada (2%); Korea (9%); Hungary (20%); Poland (10%); India (3%)

				Incidence of neutropenic complications 1. 1 (0.8%) 2. 5 (4.2%) Difference: 3.4% P value NR: 0.21	NS			

Abbreviations : AC = active comparator; AEs = adverse effects; ANC = absolute neutrophil count; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ITT = intention to treat; IWRS = interactive web response system; L = liter; MC = multi-site; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open-label; PP = per protocol; RCT = randomized controlled trial; SAEs = serious adverse effects; SC = subcutaneous; Y = years.

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25. Nyvepria (pegfilgrastim-apgf) Prescribing Information. Pfizer. New York, NY. Apr 2021.
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27. Fulphila (pegfilgrastim-jmdb) Prescribing Information. Mylan Pharmaceuticals. Morgantown, WV. Mar 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
filgrastim	NEUPOGEN	INJECTION	VIAL	Y
filgrastim	NEUPOGEN	INJECTION	SYRINGE	Y
pegfilgrastim-apgf	NYVEPRIA	SUBCUT	SYRINGE	Y
sargramostim	LEUKINE	INJECTION	VIAL	Y
eflapegrastim-xnst	ROLVEDON	SUBCUT	SYRINGE	N
filgrastim-aafi	NIVESTYM	INJECTION	VIAL	N
filgrastim-aafi	NIVESTYM	SUBCUT	SYRINGE	N
filgrastim-ayow	RELEUKO	INJECTION	VIAL	N
filgrastim-ayow	RELEUKO	SUBCUT	SYRINGE	N
filgrastim-sndz	ZARXIO	INJECTION	SYRINGE	N
pegfilgrastim	NEULASTA	SUBCUT	SYRINGE	N
pegfilgrastim	NEULASTA ONPRO	SUBCUT	SYR W/ INJ	N
pegfilgrastim-bmez	ZIEXTENZO	SUBCUT	SYRINGE	N
pegfilgrastim-cbqv	UDENYCA	SUBCUT	SYRINGE	N
pegfilgrastim-cbqv	UDENYCA AUTOINJECTOR	SUBCUT	AUTO INJCT	N
pegfilgrastim-fpgk	STIMUFEND	SUBCUT	SYRINGE	N
pegfilgrastim-jmdb	FULPHILA	SUBCUT	SYRINGE	N
pegfilgrastim-pbbk	FYLNETRA	SUBCUT	SYRINGE	N
tbo-filgrastim	GRANIX	SUBCUT	VIAL	N
tbo-filgrastim	GRANIX	SUBCUT	SYRINGE	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to June Week 5 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to July 11, 2023

1	exp Febrile Neutropenia/ or Granulocyte Colony-Stimulating Factor/	3403194
2	exp Filgrastim/	2135
3	pegfilgrastim.mp.	946
4	sargramostim.mp.	207
5	eflapegrastim.mp.	10
6	tbo-filgrastim.mp.	25
7	2 or 3 or 4 or 5 or 6	2505
8	1 and 7	2139
9	limit 8 to (english language and humans and yr="2022 -Current")	77

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ROLVEDON™ safely and effectively. See full prescribing information for ROLVEDON.

ROLVEDON™ (eflapegrastim-xnst) injection, for subcutaneous use
Initial U.S. Approval: 2022

----------INDICATIONS AND USAGE----------
Rolvedon is a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia. (1)

Limitations of Use
Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended Dose: 13.2 mg administered subcutaneously once per chemotherapy cycle. (2.1)
- Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer within the period from 14 days before to 24 hours after administration of cytotoxic chemotherapy. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 13.2 mg/0.6 mL solution in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------
Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as eflapegrastim, pegfilgrastim or filgrastim products. (4)

----------WARNINGS AND PRECAUTIONS----------
- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Rolvedon in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Rolvedon in patients with serious allergic reactions. (5.3)
- Sickle Cell Crisis in Patients with Sickle Cell Disorders: Discontinue Rolvedon if sickle cell crisis occurs. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Rolvedon if causality is likely. (5.5)
- Leukocytosis: Monitor complete blood count (CBC) during Rolvedon therapy. (5.6)
- Thrombocytopenia: Monitor platelet counts. (5.7)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using Rolvedon in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML. (5.10)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥20%) are fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Spectrum Pharmaceuticals, Inc. at 1-888-713-0688 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2022

Appendix 4: Key Inclusion Criteria

Population	Patients receiving chemotherapy
Intervention	C-CSF and GM-CSF in **Appendix 1**
Comparator	See **Appendix 1**
Outcomes	Symptom improvement, morbidity, mortality/survival, serious adverse events
Timing	Any study duration
Setting	Inpatient/outpatient combination or outpatient

Appendix 5: Summary of FDA Labeled Indications of G-CSF and CM-CSF Products

FDA Labeled Indications	Filgrastim NEUPOGEN[19]	Filgrastim-aafi NIVESTYM[20]	Filgrastim-sndz ZARXIO[21]	tbo-Filgrastim GRANIX[22]	Sargramostim LEUKINE*[23]
Decrease the **incidence** of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.	x	x	x		
In adult and pediatric patients 1 month and older for reduction in the **duration** of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.				x	
Reduce the time to neutrophil recovery and the **duration** of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).	x	x	x		
To shorten time to neutrophil recovery and to reduce the **incidence** of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with AML.					x
Reduce the **duration** of neutropenia and neutropenia-related clinical sequelae, e.g., , febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).	x	x	x		
For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic BMT in adult and pediatric patients 2 years of age and older.					x
For the acceleration of myeloid reconstitution following allogeneic BMT in adult and pediatric patients 2 years of age and older.					x

For the acceleration of myeloid reconstitution following autologous BMT or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older.					x
Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.	x	x	x		
For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients.					x
Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia	x	x	x		
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)	x				x
	Pegfilgrastim NEULASTA†[24]	**Pegfilgrastim-apgf NYVEPRIA†[25]**	**Pegfilgrastim-bmez ZIEXTENZO†[26]**	**Pegfilgrastim-cbqv UDENYCA†[2]**	**Pegfilgrastim-jmdb FULPHILA†[27]**
Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically a significant incidence of febrile neutropenia.	x	x	x	x	x
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).	x			x	
	Pegfilgrastim-fpgk STIMUFEND†[1]	**Eflapegrastim ROLVEDON†[3]**			
Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving	x	x			

myelosuppressive anti-cancer drugs associated with a clinically a significant incidence of febrile neutropenia.					
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).					

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)

[†]Limitation of Use: NOT indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.