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# 5.85.010

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| **Section:** | Prescription Drugs | **Effective Date:** | January 1, 2026 |
| **Subsection:** | Hematological Agents | **Original Policy Date:** | December 7, 2011 |
| **Subject:** | Neupogen Granix Nivestym Nypozi Releuko Zarxio | **Page:** | 1 of 10 |

***Last Review Date:*** December 12, 2025

# Neupogen Granix Nivestym Nypozi Releuko Zarxio

## Description

Neupogen (filgrastim), Granix* (tbo-filgrastim), **Nivestym** (filgrastim-aafi), Nypozi* (filgrastim-txid), Releuko (filgrastim-ayow), **Zarxio** (filgrastim-sndz)

*Prior authorization for specific formulations applies only to formulary exceptions due to being a non-covered medication.

Preferred products: Nivestym, Zarxio

**Background**
Colony stimulating factors are medications used to stimulate the production of neutrophils, a type of white blood cells important in fighting off infections. Granix (tbo-filgrastim), Neupogen (filgrastim) and Neupogen biosimilars are granulocyte colony-stimulating factors (G-CSF) that act on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Zarxio (filgrastim-sndz), Nivestym (filgrastim-aafi), Releuko (filgrastim-ayow), Nypozi (filgrastim-txid) are biosimilars to Neupogen and approved for most indications of Neupogen (1-6).

**Regulatory Status**
FDA-approved indications:

1. Cancer patients receiving myelosuppressive chemotherapy
   Filgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive

anticancer drugs associated with a significant incidence of severe neutropenia with fever (1-6).

2. Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy
   Filgrastim is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML (1-3, 5-6).

3. Cancer patients receiving bone marrow transplant
   Filgrastim is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation (1-3, 5-6).

4. Patients undergoing peripheral blood progenitor cell collection and therapy
   Filgrastim is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (1-3, 6).

5. Patients with severe congenital, cyclic or idiopathic neutropenia
   Filgrastim is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (1-3, 5-6).

6. Patients acutely exposed to myelosuppressive doses of radiation
   Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic syndrome of acute radiation syndrome) (1, 6).

Off-Label Uses: (7-11)

1. Agranulocytosis
2. AIDS associated
3. Aplastic anemia
4. Ganciclovir-induced neutropenia
5. Hairy cell leukemia
6. Hematopoietic stem cell transplantation
7. Umbilical cord stem cell transplantation
8. Hepatitis C therapy associated (ANC < 750 $mm^3$)

9. Myelodysplastic syndrome in neutropenic patients with recurrent or resistant infections

Granix is not technically considered a biosimilar to Neupogen because it was filed as a Biologics License Application since a biosimilars approval pathway had not been established at the time of FDA submission. Although these two drugs have slight structural differences, the pharmacokinetic parameters, safety, and efficacy between the two biologics do not significantly differ (12).

Splenic rupture, including fatal cases, can occur following the administration of filgrastim. Patients who report left upper abdominal or shoulder pain after receiving filgrastim should be evaluated for an enlarged spleen or splenic rupture (1-6).

Acute respiratory distress syndrome (ARDS) can occur in patients receiving filgrastim. Patients should be evaluated for ARDS if they develop fever and lung infiltrates or respiratory distress after receiving filgrastim and should be discontinued in patients with ARDS (1-6).

Serious allergic reactions, including anaphylaxis, can occur in patients receiving filgrastim. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue therapy in patients with serious allergic reactions. Do not administer filgrastim to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim (1-6).

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim (1-6).

**Related policies**
Leukine, Neulasta, Rolvedon

## Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Neupogen, Granix, Nivestym, Nypozi, Releuko, and Zarxio may be considered **medically necessary** if the conditions indicated below are met.

Neupogen, Granix, Nivestym, Nypozi, Releuko, and Zarxio may be considered **investigational** for all other indications.

## Prior-Approval Requirements

### Diagnoses

Patient must have **ONE** of the following:

1. Acute myeloid leukemia (AML)
    a. Following induction chemotherapy or consolidation chemotherapy
2. Agranulocytosis
3. Hematopoietic stem cell transplantation
4. Umbilical cord stem cell transplantation
5. Aplastic anemia
6. Hairy cell leukemia
7. Myelodysplastic syndrome in neutropenic patients with recurrent or resistant infections
8. Neutropenia
    a. AIDS associated
    b. Chemotherapy associated; prophylaxis in patients at intermediate to high risk for febrile neutropenia following chemotherapy with solid or non-myeloid malignancies
    c. Hepatitis C therapy associated (ANC < 750/$mm^3$)
    d. Chronic congenital neutropenia (e.g., Kostmann's syndrome)
    e. Cyclic neutropenia
    f. Idiopathic neutropenia
    g. Secondary to anti-rejection medications post-transplant
    h. Ganciclovir-induced neutropenia
    i. Cytomegalovirus-induced neutropenia
9. Peripheral blood progenitor cell (PBPC) collection
    a. Autologous peripheral blood progenitor cell (PBPC) mobilization and following transplantation
10. Hematopoietic syndrome of acute radiation syndrome

**AND ALL** of the following:

1. **NOT** used in combination with another granulocyte colony-stimulating factor (G-CSF)
2. **Non-preferred medications only:** Inadequate treatment response, intolerance, or contraindication to **ONE** of the preferred products (Nivestym, Zarxio)

## Prior – Approval *Renewal* Requirements

### Diagnoses

Patient must have **ONE** of the following:

1. Acute myeloid leukemia (AML)
    a. Following induction chemotherapy or consolidation chemotherapy
2. Agranulocytosis
3. Hematopoietic stem cell transplantation
4. Umbilical cord stem cell transplantation
5. Aplastic anemia
6. Hairy cell leukemia
7. Myelodysplastic syndrome in neutropenic patients with recurrent or resistant infections
8. Neutropenia
    a. AIDS associated
    b. Chemotherapy associated; prophylaxis in patients at intermediate to high risk for febrile neutropenia following chemotherapy with solid or non-myeloid malignancies
    c. Hepatitis C therapy associated (ANC < 750/$mm^3$)
    d. Chronic congenital neutropenia (e.g., Kostmann's syndrome)
    e. Cyclic neutropenia
    f. Idiopathic neutropenia
    g. Secondary to anti-rejection medications post-transplant
    h. Ganciclovir-induced neutropenia
    i. Cytomegalovirus-induced neutropenia
9. Peripheral blood progenitor cell (PBPC) collection
    a. Autologous peripheral blood progenitor cell (PBPC) mobilization and following transplantation
10. Hematopoietic syndrome of acute radiation syndrome

**AND** the following:

1. **NOT** used in combination with another granulocyte colony-stimulating factor (G-CSF)

## Policy Guidelines

### Pre - PA Allowance

None

### Prior - Approval Limits

**Duration** 6 months

### Prior – Approval *Renewal* Limits

Same as above

## Rationale

**Summary**

Colony stimulating factors are medications used to stimulate the production of neutrophils, a type of white blood cells important in fighting off infections. Granix (tbo-filgrastim), Neupogen (filgrastim) and Neupogen biosimilars are granulocyte colony-stimulating factors (G-CSF) that act on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Zarxio (filgrastim-sndz), Releuko (filgrastim-awyo), Nivestym (filgrastim-aafi), and Nypozi (filgrastim-txid) are biosimilars to Neupogen and approved for most indications of Neupogen (1-6).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Neupogen and its biosimilars while maintaining optimal therapeutic outcomes.

**References**

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5. Releuko [package insert]. Bridgewater, NJ: Amneal Biosciences, LLC.; April 2022.
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12. Lubenau H, Sveikata A, Gumbrevicius G, et al. Bioequivalence of two recombinant granulocyte colony-stimulating factor products after subcutaneous injection in healthy volunteers. *Int J Clin Pharmacol Ther*. 2009;47(4):275-282.

## Policy History

| Date | Action |
|---|---|
| July 2010 | ICD-9 code was removed for myelosuppressive chemotherapy, to decrease the incidence of infection as manifested by febrile neutropenia (various), bone marrow transplantation (996.85), peripheral blood progenitor cell collection (various), acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma, ALL or Hodgkin's disease undergoing bone marrow transplantation (various), induction chemotherapy in acute myelogenous leukemia (various), mobilization and following transplantation of autologous PBPC (various), myeloid reconstitution after allogenic bone marrow transplantation (various), severe chronic neutropenia (various) and bone marrow transplantation failure or engraftment delay (996.0-996.5). ICD-9 code was updated for bone marrow transplantation failure or engraftment delay (996.82). ICD-10 code was added for bone marrow transplantation failure or engraftment delay (T86.02). |

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| December 2010 | Simplify criterion; listing approved diagnoses in a bullet point style which is easier to read with associated lab values supported in the FDA approved packaging. Removal of Neulasta from the colony stimulating agents PA criteria due to different FDA approved indications (1). Removal of remaining ICD-9 codes due to various codes used to indicate these diagnoses. |
| September 2011 | Separating the colony stimulating agent criterion into individual agents; adding coverage for drug (non-chemotherapy) associated neutropenia for Hepatitis C treatment. Hepatitis C virus (HCV) therapy-induced neutropenia; defined as absolute neutrophil count (ANC) below 750 cells/µL. ANC typically decreases by 30-50% from normal with HCV therapy. Therefore, neutropenia is a common reason for dose reduction or withdrawal from HCV therapy (1). Treatment for neutropenia is granulocyte colony stimulating factors (G-CSF) such as Leukine. Several studies have shown that administration of G-CSF is effective in increasing neutrophil count and reducing dose reduction or withdrawal from HCV therapy, which leads to increased sustained virological response (SVR) (4,5). Not having to modify the dose of HCV therapy and an increased SVR means an improvement in the quality of life of the patient (5). Current criterion allows for treatment of AIDS associated neutropenia supported by the FDA orphan drug status approved September 3, 1991 (6). Chemotherapy associated neutropenia is supported by the American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) (7,8). Although not FDA approved; treatment of Myelodysplastic syndrome is supported by the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) (7,8). Agranulocytosis, aplastic anemia, and the use in hairy cell leukemia is supported by Micromedex (9). |
| January 2012 | Added >50 for AML; clarified ANC requirements for neutropenia. |
| December 2012 | Annual editorial review |
| March 2014 | Annual editorial review and reference update, clarified age requirement for AML to be 18 years of age and older, added cyclic and idiopathic forms of neutropenia (1), added neutropenia secondary to anti-rejection medications post-transplant (9). Decreased approval and renewal limits to 6 months |
| March 2015 | Annual editorial review and reference update |

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| | Addition of not used in combination with another granulocyte colony-stimulating factor (G-CSF) |
| April 2015 | Addition of Zarxio to PA |
| June 2015 | Removal of Zarxio from Neupogen criteria and addition of new indication Hematopoietic Syndrome of Acute Radiation Syndrome |
| September 2015 | Annual review<br>Removal of 18 years of age and older from the AML |
| December 2016 | Annual editorial review and reference update.<br>Policy code changed from 5.10.10 to 5.85.10 |
| September 2017 | Annual editorial review |
| September 2018 | Annual editorial review and reference update<br>Addition of biosimilar Nivestym<br>Addition of off-label indications to biosimilars and Granix per SME<br>Change of policy name to Neupogen Granix Nivestym Zarxio |
| November 2018 | Annual review |
| March 2019 | Annual review and reference update. Removed parentheses from around Kostmann's Syndrome indication per SME |
| December 2019 | Annual review. Addition of requirement to trial preferred products |
| March 2020 | Annual review and reference update |
| December 2020 | Annual review. Added Nivestym as a preferred product |
| March 2021 | Annual editorial review and reference update<br>Revised background and summary sections. Clarification added to the t/f, intolerance, C/I to preferred products requirement indicating that it only applies to claims adjudicated through the pharmacy benefit |
| June 2021 | Annual review and reference update |
| April 2022 | Addition of biosimilar Releuko to policy |
| June 2022 | Annual editorial review and reference update. Off-label uses references updated |
| March 2023 | Annual review and reference update. Changed policy number to 5.85.010 |
| June 2023 | Annual review and reference update |
| December 2023 | Annual review and reference update. Per FEP, changed preferred products to Nivestym and Zarxio. Also removed Medex requirements. Added t/f requirement of ONE preferred agent to initiation |
| June 2024 | Annual review and reference update |
| December 2024 | Addition of biosimilar Nypozi to policy |
| March 2025 | Annual review and reference update |
| June 2025 | Annual review and reference update |

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| December 2025 | Annual review. Per FEP, Granix moved to require FE+PA |

Keywords

**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 12, 2025 and is effective on January 1, 2026.**