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Section:	Prescription Drugs	**Effective Date:**	July 1, 2024
Subsection:	Hematological Agents	**Original Policy Date:**	December 7, 2011
Subject:	Neupogen Granix Nivestym Releuko Zarxio	**Page:**	1 of 10

Last Review Date: June 13, 2024

Neupogen Granix Nivestym Releuko Zarxio

Description

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

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), and Releuko (filgrastim-ayow) are biosimilars to Neupogen and approved for most indications of Neupogen. The FDA defines biosimilar as a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product (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 (1-5).

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).

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).

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).

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. 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).

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

The FDA defines biosimilar as a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. A manufacturer developing a proposed biosimilar demonstrates that its product is highly similar to the reference product by extensively analyzing the structure and function of both the reference product and the proposed biosimilar. Minor differences between the reference product and the proposed biosimilar in clinically inactive components are acceptable. Manufacturers must also demonstrate that its proposed biosimilar has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness) (6).

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 (1-5).

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 (1-5).

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 (1-5).

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim (1-5).

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

Neupogen, Granix, Nivestym, 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), and Nivestym (filgrastim-aafi) are biosimilars to Neupogen and approved for most indications of Neupogen. The FDA defines biosimilar as a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product (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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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).
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 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 Removal of 18 years of age and older from the AML
December 2016	Annual editorial review and reference update. Policy code changed from 5.10.10 to 5.85.10
September 2017	Annual editorial review
September 2018	Annual editorial review and reference update Addition of biosimilar Nivestym Addition of off-label indications to biosimilars and Granix per SME 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 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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 13, 2024 and is effective on July 1, 2024.