Neupogen Granix Nivestym Zarxio

Description

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

Bolded medications are the preferred products

Background

Neupogen is a man-made form of granulocyte colony-stimulating factor (G-CSF), which is made using the bacteria *Escherichia coli*. G-CSF is a substance naturally produced by the body. It stimulates the growth of neutrophils, a type of white blood cell important in the body’s fight against infection (1).

Zarxio and Nivestym are leukocyte growth factors which are biosimilar to Amgen Inc.’s Neupogen (filgrastim), and approved for most indications as Neupogen. Zarxio and Nivestym are granulocyte colony-stimulating factors (G-CSF), which are made using the bacteria *Escherichia coli*. G-CSF is a substance naturally produced by the body. It stimulates the growth of neutrophils, a type of white blood cell important in the body’s fight against infection (2-3).

Granix is a short-acting human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. G-CSF is a naturally occurring hormone that is produced by the body to stimulate the bone marrow to produce neutrophils, a type of white blood cell that helps the immune system fight infection. A recombinant form of G-CSF is used to treat certain cancer patients with neutropenia in order to stimulate the bone marrow to produce more white blood cells. Granix binds to G-CSF receptors and stimulates proliferation of neutrophils and increase neutrophil counts and activity (4).
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 (1-4).

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 (1-4).

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 (1-4).

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 (1-4).

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 (1-4).

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, 5-6).

Off-label Use

Neutropenia secondary to anti-rejection medications post-transplant (7). A study by Hornedo determined the role of granulocyte colony stimulating factor (G-CSF) following transplantation in the post-transplant period. Patients receiving G-CSF reached 500 and 1,000 neutrophils
significantly faster (P=0.001) than patients with no G-CSF. G-CSF accelerates the time to neutrophil engraftment. This translated into a significantly (P<0.05) shorter hospitalization time for patients receiving G-CSF (8). In kidney and liver transplant recipients, granulocyte colony-stimulating factor has been used successfully to reverse ganciclovir-induced neutropenia or cytomegalovirus-induced neutropenia (9).

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) (5).

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 (6).

Splenic rupture, including fatal cases, can occur following the administration of filgrastim. Patients who report left upper abdominal or shoulder pain after receiving Neupogen should be evaluated for an enlarged spleen or splenic rupture (1-4).

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 Neupogen and should be discontinued in patients with ARDS (1-4).

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 (1-4).
Severe sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim (1-4).

**Related policies**

Leukine, Neulasta/Fulphila

**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, and Zarxio may be considered **medically necessary** for the indications listed below.

Neupogen, Granix, Nivestym, 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 < 750mm³)
d. Chronic Congenital 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)

   2. Neupogen and Nivestym only: Patient MUST have tried ALL preferred products (Granix and Zarxio) unless the patient has a valid medical exception (e.g. inadequate treatment response, intolerance, contraindication)

Prior – Approval Renewal Requirements

Same as above

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 6 months

Prior – Approval Renewal Limits

Duration 6 months

Rationale

Summary

Neupogen, Granix, Nivestym, and Zarxio are recombinant human granulocyte-macrophage colony stimulating factor (rhu G-CSF) produced by Escherichia coli (E coli) bacteria. They are FDA approved for use in myelosuppressive chemotherapy, AML receiving chemotherapy, bone
marrow transplant, harvesting of peripheral blood stem cells and severe chronic neutropenia (1-3).

Zarxio and Nivestym are biosimilars to Neupogen (filgrastim) and are approved for the same indications as Neupogen (5). Granix, while not technically a biosimilar, does not significantly differ from Neupogen in terms of the pharmacokinetic parameters, safety, and efficacy (6).

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Neupogen, Granix, Nivestym, and Zarxio while maintaining optimal therapeutic outcomes.

References
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
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
December 2016 Annual editorial review and reference update.
September 2017 Annual editorial review
September 2018 Annual editorial review and reference update
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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 6, 2019 and is effective on January 1, 2020.