Policy Title:	Short Acting Granulocyte Colony Stimulating Factors: Nivestym (filgrastim-aafi), Neupogen (filgrastim), Nypozi (filgrastim-txid), Granix (tbo-filgrastim), Releuko (filgrastim-ayow), Zarxio (filgrastim-sndz) **NON-ONCOLOGY POLICY**		
		Department:	PHA
Effective Date:	01/01/2020		
Review Date:	04/19/2019, 09/18/2019, 12/13/2019, 1/29/2020, 8/3/2020, 7/22/2021, 6/16/2022, 10/6/2022, 2/9/2023, 12/07/2023, 01/04/2024, 09/30/2025		

Purpose: To support safe, effective and appropriate use of short-acting Granulocyte Colony Stimulating Factors.

Scope: Medicaid, Commercial, Medicare

Policy Statement:

Colony Stimulating Factors are covered under the Medical Benefit when used within the following guidelines. Use outside of these guidelines may result in non-payment unless approved under an exception process. Zarxio (filgrastim-sndz) is the preferred short-acting Colony Stimulating Factor. **For oncology indications, please refer to Myeloid Growth Factors Policy.**

Procedure:

Coverage of short-acting Colony Stimulating Factors will be reviewed prospectively via the prior authorization process based on criteria below.

Initial Criteria:

- Member has one of the following conditions:
  - Bone marrow transplant (BMT); OR
  - Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant (Nivestym/Neupogen-ONLY); OR
  - Peripheral Blood Stem Cell (PBSC) mobilization and transplant (Granix- ONLY); OR
  - Severe chronic neutropenia (Nivestym/Neupogen- ONLY);
    - Member must have an absolute neutrophil count (ANC) < 500/mm^3; AND
    - Member must have a diagnosis of one of the following:
      - Congenital neutropenia; OR
      - Cyclic neutropenia; OR
      - Idiopathic neutropenia; OR
  - Bone Marrow Transplantation (BMT) failure or Engraftment Delay; AND
- Members must have a documented failure, contraindication, or intolerance to Zarxio (filgrastim-sndz) OR for members that are currently on treatment with Nivestym (filgrastim-aafi), Neupogen (filgrastim), Nypozi (filgrastim-txid), Releuko (filgrastim-ayow), or Granix (tbo-filgrastim) can remain

on treatment OR Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements

Coverage Duration: 4 months

Per §§ 42 CFR 422.101, this clinical medical policy only applies to Medicare in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD).

Policy Rationale:
Nivestym, Neupogen, Nypozi**,** Granix, Releuko, and Zarxio were reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Nivestym, Neupogen, Granix, Releuko, and Zarxio according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using these drugs for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For Medicare members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.

Dosage/Administration:

Indication	**Dose**	**Maximum dose (1 billable unit = 1 mcg)**
BMT/PBPC	• 10mcg/kg daily for up to 14 days	• 1200 billable units per day
Severe Chronic Neutropenia	• 5 mcg/kg daily for up to 14 days for idiopathic or cyclic neutropenia • 6mcg/kg twice daily for severe congenital neutropenia	• 1380 billable units per day
All other indications	• 5mcg/kg daily for up to 14 days	• 600 billable units per day

Investigational use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

Applicable Codes:
Below is a list of billing codes applicable for covered treatment options. The below tables are provided for reference purposes and may not be all-inclusive. Requests received with codes from tables below do not guarantee coverage. Requests must meet all criteria provided in the procedure section.

The following HCPCS/CPT codes are:

HCPCS/CPT Code	Description
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio)
J1442	Injection, filgrastim (g-csf), excludes biosimilar, 1microgram
J1447	Injection, tbo-filgrastim, 1 microgram
Q5110	Injection, filgrastim-aafi, biosimilar, (nivestym), 1 microgram
Q5148	Injection, filgrastim-txid **(**Nypozi) biosimiliar. 1 microgram
Q5125	Injection, filgrastim-ayow, biosimilar, (releuko), 1 microgram

Summary of Evidence:

Nivestym (filgrastim-aafi)
Nivestym (filgrastim-aafi) is a short-acting granulocyte colony-stimulating factor (G-CSF) biosimilar to Neupogen (filgrastim). It 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. Nivestym acts by binding to G-CSF receptors on hematopoietic cells, stimulating neutrophil proliferation and differentiation, thereby enhancing host defect against infection. Clinical efficacy of Nivestym was demonstrated in multiple randomized controlled trials. In severe chronic neutropenia, it markedly increased ANC and reduced infection rates. Overall, Nivestym demonstrated clinical efficacy equivalent to Neupogen across all approved indications. Common adverse reactions include bone pain, pyrexia, rash, headache, cough, and dyspnea.

Neupogen (filgrastim)
Neupogen (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. Neupogen is a recombinant human granulocyte colony-stimulating factor (G-CSF). Neupogen binds G-CSF receptors on hematopoietic cells, stimulating proliferation, differentiation, and functional activation of neutrophils. Clinical efficacy was demonstrated in multiple randomized controlled trials, and the median duration of severe neutropenia was reduced from six to two days ($p<0.001$), with improved ANC nadir and earlier neutrophil recovery. Common adverse reactions include bone pain, nausea, headache, fatigue, and injection site reactions.

Nypozi (filgrastim-txid)
Nypozi (filgrastim-txid) is a short-acting granulocyte colony-stimulating factor (G-CSF) biosimilar to Neupogen indicated to (1) decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignances receiving myelosuppressive chemotherapy; (2) reduce time to neutrophil recovery and fever duration in AML after induction or consolidation; (3) reduce duration of neutropenia and related sequelae following myeloablative chemotherapy with bone marrow transplantation; (4) mobilize autologous hematopoietic progenitor cells for leukapheresis; (5) reduce sequalae of severe chronic neutropenia; and (6) increase survival after myelosuppressive

radiation exposure (Heme-ARS). Nypozi binds the G-CSF receptor on hematopoietic cells to stimulate neutrophil proliferation, differentiation, and function. Nypozi demonstrated efficacy comparable to reference pegfilgrastim in reducing the duration of severe neutropenia in patients receiving myelosuppressive chemotherapy. In a randomized, double-blind, active-controlled phase 3 trial of 406 patients with breast cancer receiving docetaxel, doxorubicin, and cyclophosphamide, the mean duration of severe neutropenia in cycle 1 was 1.0 day with Nypozi and 1.1 days with pegfilgrastim, meeting criteria for equivalence. Rates of febrile neutropenia, infection, and adverse events were also comparable between groups. Overall, Nypozi demonstrated equivalent safety and efficacy to the reference product in preventing chemotherapy-induced neutropenia. The most common adverse effects include pyrexia, pain, rash, cough, dyspnea, and bone pain/headache.

Releuko (filgrastim-ayow)

Releuko is a short-acting granulocyte colony-stimulating factor (G-CSF) biosimilar to Neupogen indicated to: (1) decrease the incidence of infection (febrile neutropenia) in patients with non-myeloid malignances receiving myelosuppressive chemotherapy; (2) reduce time to neutrophil recovery and duration of fever in AML after induction or consolidation; (3) reduce duration of neutropenia and related sequelae after myeloablative chemotherapy with bone marrow transplantation; (4) mobilize autologous hematopoietic progenitor cells for leukapheresis; (5) reduce sequelae of severe chronic neutropenia; and (6) increase survival after myelosuppressive radiation syndrome. Releuko binds the G-CSF receptor on hematopoietic cells to stimulate proliferation, differentiation, and activation of neutrophils. Releuko demonstrated equivalent safety and efficacy to the reference product Neupogen in multiple randomized, placebo-controlled trials across all approved indications. In patients with cancer receiving myelosuppressive chemotherapy, Releuko significantly reduced the incidence of febrile neutropenia (40% vs 76%; $p < 0.001$), as well as the duration and severity of neutropenia, hospitalizations, and antibiotic use. Overall, Releuko demonstrated clinical equivalence to Neupogen in accelerating neutrophil recovery and reducing neutropenia-associated complications. The most common adverse effects include pyrexia, pain, rash, cough, dyspnea, and bone pain/headache.

Granix (tbo-filgrastim)

Granix is a short-acting granulocyte colony-stimulating factor (G-CSF) indicated to reduce the duration of severe neutropenia in adults and pediatric patients ≥1 month with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia. In clinical experience, Granix demonstrated safety and efficacy comparable to filgrastim in reducing chemotherapy-induced neutropenia. In a phase 3, multicenter, randomized trial of 348 patients with stage II-IV breast cancer receiving doxorubicin and docetaxel, Granix significantly shortened the duration of severe neutropenia to 1.1 days vs 3.8 days with placebo ($p < 0.0001$). Overall, Granix was well tolerated and effectively accelerated neutrophil recovery, and decreasing infection risk. It stimulates neutrophil proliferation, differentiation, and function via G-CSF receptor binding. The most common adverse reaction is bone pain.

Zarxio (filgrastim-sndz)

Zarxio is a short-acting granulocyte colony-stimulating factor (G-CSF) biosimilar to Neupogen indicated to (1) decrease the incidence of infection (febrile neutropenia) in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy; (2) reduce time to neutrophil recovery and duration of fever in AML following induction or consolidation chemotherapy; (3) reduce duration of

neutropenia and neutropenia-related sequalae after myeloablative chemotherapy with bone marrow transplantation; (4) mobilize autologous hematopoietic progenitor cells for collection by leukapheresis; (5) reduce sequelae of severe chronic neutropenia; and (6) increase survival after acute exposure to myelosuppressive doses of radiation. Zarxio binds the G-CSF receptor on hematopoietic cells to stimulate neutrophil proliferation, differentiation, and function. Zarxio demonstrated safety and efficacy comparable to Neupogen across all approved indications. In a pivotal phase 3, randomized, double-blind, placebo-controlled trial of patients with small cell lung cancer receiving myelosuppressive chemotherapy (cyclophosphamide, doxorubicin, and etoposide), Zarxio significantly reduced the incidence of febrile neutropenia (40% vs 76%; $p < 0.001$) and the duration and severity of neutropenia, as well as hospitalizations and antibiotic use. Overall, Zarxio effectively accelerated neutrophil recovery and demonstrated equivalent clinical efficacy and safety to the reference filgrastim product. Common adverse reactions include pyrexia, pain, rash, cough, dyspnea; bone pain, pyrexia, and headache.

References:

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6. Kelaidi C Beyne-Rauzy O, Braun T, et al. High Response rate and improved exercise capacity and quality of life with a new regimen of darbepoetin alfa with or without filgrastim in lower-risk myelodysplastic syndromes: a phase II study by the GFM. Ann Hematol 2013; 92:621-631.
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8. National Government Services, Inc. Local Coverage Article: Filgrastim, Pegfilgrastim, Tbo-filgrastim, Filgrastim-sndz (e.g., Neupogen®, Neulasta™, Granix™, Zarxio™) - Related to LCD L33394 (A52408). Centers for Medicare & Medicaid Services, Inc. Updated on 7/06/2018 with effective date 7/15/2018. Accessed July 2018.
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