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

RATIONALE FOR INCLUSION IN PA PROGRAM

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**
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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).
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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
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filgrastim (1-4).

Summary
Neupogen, Granix, Nivestym, and Zarxio are recombinant human granulocyte-macrophage colony stimulating factor (rhu G-CSF) produced by *Eschericoli 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
Neupogen (filgrastim), Granix (tbo-filgrastim),
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the post-transplant period. Bone Marrow Transplant. 2002 May; 29(9):737-43.

stimulating factor, and other immunomodulatory therapies for the treatment of infectious