OVERVIEW
Colony stimulating factors (CSFs) are biosynthetic products that stimulate the development of white blood cells such as neutrophils and macrophages (infection-fighting blood cells). Neutropenia is a severe drop in infection-fighting white blood cells (neutrophils). Neutrophils are measured in terms of “absolute neutrophil count” (ANC). CSF administration decreases the frequency and duration of hospitalization and anti-infective therapy by increasing the number of infection-fighting cells in conditions such as chemotherapy-induced neutropenia (reduction in the neutrophil count after chemotherapy), bone marrow transplantation (BMT), severe chronic neutropenia (low white cell blood count), and myelodysplasia (disorder of blood cell production). When CSFs are used in conjunction with chemotherapy, it is possible to maintain or even increase doses of chemotherapeutic agents. In patients with HIV infection, CSFs correct or minimize drug-induced or disease-induced neutropenia.

POLICY STATEMENT
Prior approval is required for prescription benefit coverage of Granix, Leukine, Neulasta, Neupogen, and Zarxio. Because of the specialized skills required for evaluation and diagnosis of patients treated with Granix, Leukine, Neulasta, Neupogen, and Zarxio as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Granix, Leukine, Neulasta, Neupogen, and Zarxio to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for duration of 6 months.

Medications
Granix® (tbo-filgrastim injection)
Leukine® (sargramostim injection)
Neulasta® (pegfilgrastim injection for subcutaneous use)
Neupogen® (filgrastim injection)
Zarxio™ (filgrastim-sndz injection for subcutaneous [SC] or intravenous [IV] use)

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of colony stimulating factors is recommended in those who meet the following criteria:

I. Granix:

FDA-Approved Indications
1. Cancer Patients Receiving Myelosuppressive Chemotherapy who are Adults.

Criteria. The patient must meet the following criteria (A, and B):
A) The agent is prescribed by, or in consultation with, an oncologist or hematologist; AND
B) The patient meets ONE of the following conditions (i, ii, iii, or iv):
   i. The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR
ii. The patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia but the risk is less than 20% based on the chemotherapy regimen and the patient has one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., aged ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus [HIV] infection); OR

iii. The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (e.g., Granix, Neulasta® [pegfilgrastim injection], Neupogen® [filgrastim injection], Zarxio™ [filgrastim-sndz injection], Leukine® [sargramostim injection]) and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR

iv. The patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescribing physician (e.g., sepsis syndrome; age > 65 years; severe neutropenia [absolute neutrophil count < 100 cells/mm³]; neutropenia expected to be > 10 days in duration; invasive fungal infection; other clinically documented infections; prior episode of febrile neutropenia).

**Dosing in Adults with Cancer Receiving Myelosuppressive Chemotherapy.** Dosing must meet the following: The dose is 5 mcg per kg per day by SC injection.

II. Leukine:

**FDA-APPROVED INDICATIONS**

1. **Acute Myelogenous Leukemia (AML).**

   **Criteria.** *Patient must meet the following criteria:* Leukine is prescribed by, or in consultation with, an oncologist or hematologist.

   **Dosing in AML:** Dosing must meet the following: The dose is 250 mcg/m² per day given IV over a 4-hour period. The dose should start after the completion of induction chemotherapy. Additional doses of induction chemotherapy may be needed. Consolidation chemotherapy may follow with Leukine being given after completion of chemotherapy.

2. **Peripheral Blood Progenitor Cell (PBPC) Collection in Patients with Cancer (Adults and Children) or Patients with Cancer (Adults and Children) who have Received Therapy with PBPC (Autologous):**

   **Criteria.** *Patient must meet the following criteria:* Leukine is prescribed by, or in consultation with, an oncologist, a hematologist, or a physician that specializes in transplantation.

   **Dosing in Patients with Cancer Undergoing Mobilization of PBPC:** Dosing must meet the following (A OR B): A) 250 to 500 mcg/m² per day administered IV over 24 hours or SC once daily; OR
B) 7.5 mcg/kg SC once daily.

**Dosing in Patients with Cancer Post PBPC Transplantation (Autologous):** Dosing must meet the following (A OR B):

A) 250 mcg/m² per day administered IV over 24 hours or SC once daily; OR

B) 7.5 mcg/kg once daily SC.

**Other Uses with Supportive Evidence**

3. **Patients with Cancer Receiving Myelosuppressive Chemotherapy.**

**Criteria.** The patient must meet the following criteria (A and B):

A) The agent is prescribed by, or in consultation with, an oncologist or hematologist; AND

B) The patient meets ONE of the following conditions (i, ii, iii, or iv):

i. The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR

ii. The patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia but the risk is less than 20% based on the chemotherapy regimen and the patient has one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., aged ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus [HIV] infection); OR

iii. The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (Neupogen® [filgrastim injection], Zarxio™ [filgrastim-sndz injection], Neulasta® [pegfilgrastim injection], Granix™ [tbo-filgrastim injection], Leukine) and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR

iv. The patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescribing physician (e.g., neutropenia expected to be > 10 days in duration; severe neutropenia [ANC < 100 cells/mm³], age greater than 65 years; prior episode of febrile neutropenia; invasive fungal infection, and other clinically documented infections).

**Dosing in Patients with Cancer Receiving Myelosuppressive Chemotherapy.** Dosing must meet the following: The dose is 250 mcg/m² per day by SC injection.

4. **Treatment of Myelodysplastic Syndrome (MDS) in Adults.**

**Criteria.** The patient must meet the following criteria: Leukine is prescribed by, or in consultation with, an oncologist or hematologist.

**Dosing in MDS in Adults.** Dosing must meet ONE of the following (A, B OR C):
A) Leukine 15 to 500 mcg/m² once daily by IV infusion over 1 to 12 hours; OR
B) Leukine 30 to 500 mcg/m² given by continuous IV infusion over 24 hours; OR
C) Leukine 125 to 250 mcg/m² SC once daily.

5. Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).

Criteria. The patient must meet the following criteria: Leukine is prescribed by, or in consultation with, a physician with expertise in treating acute radiation syndrome.

Dosing in Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome): Dosing must meet the following: 250 mcg/m² SC once daily.

III. Neulasta:

FDA-APPROVED INDICATIONS

1. Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy.

Criteria. The patient must meet the following criteria (A and B):
A) The agent is prescribed by, or in consultation with, an oncologist or hematologist; AND
B) The patient meets ONE of the following conditions (i, ii, or iii):
   i. The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (i.e., the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR
   ii. The patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia but the risk is less than 20% based on the chemotherapy regimen and the patient has one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., aged ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal function; poor performance status; or human immunodeficiency virus [HIV] infection); OR
   iii. The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (Leukine® [sargramostim injection], Neulasta, Neupogen® [filgrastim injection], Zarxio™ [filgrastim-sndz injection] and Granix® [tbo-filgrastim injection]) and a reduced dose or frequency of chemotherapy may compromise treatment outcome.

Dosing in Patients with Cancer Receiving Myelosuppressive Chemotherapy: Dosing must meet ONE of the following (A, B OR C):
A) In adults, the dose is a single SC injection of 6 mg administered once per chemotherapy cycle; OR
B) In children, a single 100 mcg per kg dose is given SC once per chemotherapy cycle; maximum dose is 6 mg.
C) For pediatric patients < 45 kg give a single SC dose once per chemotherapy cycle as follows: 4 mg (0.4 mL) is recommended in patients 31 to 44 kg; 2.5 mg (0.25 mL) is recommended for patients 21 to 30 kg; 1.5 mg (0.15 mL) is recommended for patients 10 to 20 kg; and 0.1 mg/kg (0.01 mL/kg) is recommended for patients < 10 kg. Of note, the Neulasta prefilled syringe is not designed to allow for direct administration of doses < 0.6 mL (6 mg). The syringe does not bear graduation marks, which are needed to accurately measure doses of Neulasta < 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of < 0.6 mL (6 mg) is not recommended due to the potential for errors.

2. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).**

   **Criteria.** *The patient must meet the following criteria:* Neulasta is prescribed by, or in consultation with, a physician with expertise in treating acute radiation syndrome.

   **Dosing in Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome):** *Dosing must meet ONE of the following (A OR B):*
   
   **A)** Two doses, 6 mg each, given SC 1 week apart; OR
   
   **B)** For pediatric patients < 45 kg give two doses SC 1 week apart as follows: 4 mg (0.4 mL) for patients 31 to 44 kg; 2.5 mg (0.25 mL) for patients 21 to 30 kg; 1.5 mg (0.15 mL) for patients 10 to 20 kg; and 0.1 mg/kg (0.01 mL/kg) is recommended for pediatric patients < 10 kg. Of note, the Neulasta prefilled syringe is not designed to allow for direct administration of doses < 0.6 mL (6 mg). The syringe does not bear graduation marks, which are needed to accurately measure doses of Neulasta < 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of < 0.6 mL (6 mg) is not recommended due to the potential for errors.

Other Uses with Supportive Evidence

3. **Patients with Cancer Following Peripheral Blood Progenitor Cell (PBPC) Transplantation.**

   **Criteria.** *The patient must meet the following criteria:* Neulasta is prescribed by, or in consultation with, an oncologist, a hematologist, or a physician that specializes in transplantation.

   **Dosing in Patients with Cancer Following PBPC Transplantation.** *Dosing must meet ONE of the following (A OR B):*
   
   **A)** The dose in adults is 6 mg SC on Day +1 or up to Day +5 after PBPC transplantation; OR
   
   **B)** The dose in children is 100 mcg per kg or 200 mcg per kg SC one time.

IV. **Neupogen and Zarxio:**

FDA-Approved Indications
1. **Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy.**

**Criteria.** *The patient must meet the following criteria (A and C):*

A) The Neupogen or Zarxio is prescribed by, or in consultation with, an oncologist or hematologist; AND

B) The patient meets ONE of the following conditions (i, ii, iii, or iv):
   
   v. The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR

   vi. The patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia but the risk is less than 20% based on the chemotherapy regimen and the patient has one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., aged ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus [HIV] infection); OR

   vii. The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (e.g., Granix™ [tbo-filgrastim injection], Leukine® [sargramostim injection], Neulasta® [pegfilgrastim injection], Neupogen, Zarxio) and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR

   viii. The patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescribing physician (e.g., sepsis syndrome; age > 65 years; severe neutropenia [absolute neutrophil count {ANC} < 100 cells/mm³]; neutropenia expected to be > 10 days in duration; invasive fungal infection; other clinically documented infections).

**Dosing in Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy.** *Dosing must meet the following:* The starting dose is 5 mcg per kg per day by SC or IV injection for up to 2 weeks. Doses may be increased in increments of 5 mcg per kg according to the duration and severity of the absolute neutrophil count (ANC) nadir after chemotherapy.

2. **Adults with Acute Myeloid Leukemia (AML) Receiving Chemotherapy.**

**Criteria.** *The patient must meet the following criteria:* Neupogen or Zarxio is prescribed by, or in consultation with, an oncologist or hematologist.

**Dosing in AML.** *Dosing must meet the following:* The starting dose is 5 mcg per kg per day by SC or IV injection for up to 2 weeks and starting 24 hours after the last dose of chemotherapy until neutrophil recovery that is usually for a maximum of 35 days. Doses may be increased in increments
of 5 mcg per kg according to the duration and severity of the absolute neutrophil count (ANC) nadir after chemotherapy.
3. **Patients with Cancer Receiving Bone Marrow Transplant (BMT).**

**Criteria.** *The patient must meet the following criteria:* Neupogen or Zarxio is prescribed by, or in consultation with, a hematologist, an oncologist, or a physician that specializes in transplantation.

**Dosing in BMT.** *Dosing must meet the following:* 10 mcg per kg per day given as an IV infusion no longer than 24 hours. During the period of neutrophil recovery, the dose should be titrated according to the absolute neutrophil count (ANC). Doses up to 30 mcg per kg per day have been used. Alternative dosing will be assessed individually on a case-by-case basis.

4. **Patients (Adults and Children) Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy.**

**Criteria.** *Patient must meet the following criteria:* Neupogen or Zarxio is prescribed by, or in consultation with, an oncologist, a hematologist, or a physician that specializes in transplantation.

**Dosing in Patients (Adults and Children) Undergoing PBPC Collection and Therapy.** *Dosing must meet ONE of the following (A, B, OR C):*

A) Patients with Cancer or Healthy Donors Undergoing Mobilization for PBPC: 10 mcg per kg per day SC, either as a bolus or continuous infusion for 5 to 7 days. Some patients may require up to 32 mcg per kg per day SC. Dosing can be once daily or twice daily. Alternate dosing will be assessed individually on a case-by-case basis.

B) Patients Undergoing Mobilization of PBPC Who Are Poor Mobilizers: 12.5 to 50 mcg per kg per day IV or SC. Dosing can be once daily or twice daily. Alternate dosing will be assessed individually on a case-by-case basis.

C) Patients with Cancer Post Autologous PBPC Transplantation: 5 to 24 mcg per kg per day after reinfusion of the collected cells until a sustainable ANC is attained. Dosing can be once daily or twice daily. Alternative dosing will be assessed individually on a case-by-case basis.
5. **Patients (Adults and Children) with Severe Chronic Neutropenia (e.g., Congenital Neutropenia, Cyclic Neutropenia, Idiopathic Neutropenia).**

**Criteria.** The patient must meet the following criteria: Neupogen or Zarxio is prescribed by, or in consultation with, a hematologist.

**Dosing in Severe Chronic Neutropenia.** Dosing must meet the following: The starting dose in congenital neutropenia is 6 mcg per kg twice daily (BID) by SC injection. For idiopathic or cyclic neutropenia, the starting dose is 5 mcg per kg SC once daily. The dose is adjusted based on the clinical response and the ANC. Alternative dosing will be assessed individually on a case-by-case basis.

6. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).**

**Criteria.** The patient must meet the following criteria: Neupogen is prescribed by, or in consultation with, a physician with expertise in treating acute radiation syndrome.

**Dosing in Patients with Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Dosing must meet the following: 10 mcg per kg per day SC.

**Other Uses with Supportive Evidence**

7. **Neutropenia Associated with Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS) in Adults.**

**Criteria.** Patient must meet the following criteria: Neupogen or Zarxio is prescribed by, or in consultation with, a physician that specializes in infectious diseases, a hematologist, or a physician that specializes in the management of HIV/AIDS.

**Dosing for Neutropenia in Adults with HIV or AIDS.** Dosing must meet the following: Neupogen or Zarxio 5 to 10 mcg per kg SC once per day.

8. **Treatment of Myelodysplastic Syndrome (MDS) in Adults.**

**Criteria.** Patient must meet the following criteria: Neupogen or Zarxio is prescribed by, or in consultation with, an oncologist or hematologist.

**Dosing in MDS.** Dosing must meet the following: The dose range of Neupogen or Zarxio is 1 to 2 mcg per kg given 1 to 2 times per week SC or 5 mcg per kg once daily SC or IV.
9. **Aplastic Anemia (Adults and Children).**

   **Criteria.** *The patient must meet the following criteria:* Neupogen or Zarxio is prescribed by, or in consultation with, a hematologist.

   **Dosing in Aplastic Anemia.** *Dosing must meet the following:* Neupogen or Zarxio 5 mcg per kg per day SC once daily or 1 to 3 times per week SC.

10. **Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia.**

    **Criteria.** Approve Neupogen or Zarxio.

    **Dosing in Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia.** *Dosing must meet the following:* The dose range is 5 to 10 mcg per kg per day SC or 300 mcg per day SC once daily.

11. **Acute Lymphocytic Leukemia (ALL).**

    **A) Criteria.** *The patient must meet the following criteria:* Neupogen or Zarxio is prescribed by, or in consultation with, an oncologist or hematologist.

    **Dosing in ALL:** *Dosing must meet the following:* Neupogen or Zarxio dose is in the range of 5 to 10 mcg per kg per day SC.

12. **Radiation-Induced Neutropenia.**

    **Criteria.** *Patient must meet the following criteria (A and B).*
    A) Neupogen or Zarxio is prescribed by, or in consultation with, an oncologist, radiologist, or radiation oncologist; AND
    B) The patient is not concurrently receiving chemotherapy.

    **Dosing in Radiation-Induced Neutropenia.** *Dosing must meet the following:* The dose of Neupogen or Zarxio is 5 mcg per kg per day SC or 300 mcg SC daily.

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**
Colony Stimulating Factors have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.
Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

2. **Concomitant use of Colony Stimulating Factors**: Colony Stimulating Factors are not recommended as combination therapy.

**Approval Duration**: 6 months

**References**