Indications:

Neupogen:
- Febrile neutropenia prophylaxis
  - In non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation
  - In non-myeloid malignancies following myelosuppressive chemotherapy
  - In patients with acute myeloid leukemia receiving chemotherapy
- Harvesting of peripheral blood stem cells
  - Mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Congenital, cyclic, or idiopathic neutropenia
  - To reduce the incidence and duration of neutropenia sequelae, including fever, infections, or oropharyngeal ulcers, in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
- Radiation injury of bone marrow, acute exposure of myelosuppressive radiation doses
  - To increase survival in patients with acute exposure to myelosuppressive doses of radiation (greater than 2 Gray)
- Other indications *(non-FDA approved)*:
  - For the treatment of HIV-induced, or drug therapy-induced neutropenia
  - Treatment of neutropenia in patients with myelodysplastic syndrome
  - For the adjunctive treatment of aplastic anemia (with cyclosporine, Thymoglobulin, and/or steroids)
  - As primary prophylaxis for febrile neutropenia and to reduce the time to neutrophil recovery and duration of febrile neutropenia following induction or consolidation chemotherapy for acute lymphoid leukemia (ALL)

Zarxio:
- Febrile neutropenia prophylaxis
  - In non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation
  - In non-myeloid malignancies following myelosuppressive chemotherapy
  - In patients with acute myeloid leukemia receiving chemotherapy
- Harvesting of peripheral blood stem cells
  - Mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
- Congenital, cyclic, or idiopathic neutropenia
Leukine:

○ To reduce the incidence and duration of neutropenia sequelae, including fever, infections, or oropharyngeal ulcers, in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

● Other indications (non-FDA approved):
  ○ For the treatment of HIV-induced, or drug therapy-induced neutropenia
  ○ Treatment of neutropenia in patients with myelodysplastic syndrome
  ○ For the adjunctive treatment of aplastic anemia (with cyclosporine, Thymoglobulin, and/or steroids)
  ○ As primary prophylaxis for febrile neutropenia and to reduce the time to neutrophil recovery and duration of febrile neutropenia following induction or consolidation chemotherapy for acute lymphoid leukemia (ALL)

Neulasta:

● For prophylaxis of chemotherapy-induced neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy

● Other indications (non-FDA approved)
  ○ Febrile neutropenia prophylaxis
    ▪ In patients with non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation
    ▪ In patients with non-myeloid malignancies following myelosuppressive chemotherapy
    ▪ In patients with acute myeloid leukemia receiving chemotherapy

Granix:

● Febrile neutropenia prophylaxis
  ○ In patients with non-myeloid malignancies following myelosuppressive chemotherapy
  ○ Other indications (non-FDA approved)
    ▪ For the treatment of HIV-induced, or drug therapy-induced neutropenia
    ▪ Treatment of neutropenia in patients with myelodysplastic syndrome
    ▪ For the adjunctive treatment of aplastic anemia (with cyclosporine, Thymoglobulin, and/or steroids)
    ▪ As primary prophylaxis for febrile neutropenia and to reduce the time to neutrophil recovery and duration of febrile neutropenia following induction or consolidation chemotherapy for acute lymphoid leukemia (ALL)
    ▪ Treatment of neutropenia in patients who did NOT receive prophylaxis:
      – Patient has risk factors for poor outcomes resulting from febrile neutropenia (e.g., age > 65, sepsis, severe neutropenia (ANC< 100/mcL), current infection, hospitalized at onset of fever, prior episode of febrile neutropenia)

Leukine:

● Following induction chemotherapy in acute myelogenous leukemia
  ○ In patients 55 years of age and older, to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death

● Mobilization and following transplantation of autologous peripheral blood progenitor cells
  ○ To allow for collection (by leukapheresis) of increased numbers of progenitor cells capable of engraftment

● Myeloid reconstitution after autologous bone marrow transplantation
- For acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT)
- Myeloid reconstitution after allogeneic bone marrow transplantation
  - For acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors
- Bone marrow transplantation failure or engraftment delay
  - In patients who have undergone allogeneic or autologous bone marrow transplantation (BMT) in whom engraftment is delayed or has failed
- Other indications (**non-FDA approved**)
  - Febrile neutropenia prophylaxis
    - In non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation
    - In non-myeloid malignancies following myelosuppressive chemotherapy
    - In patients with acute myeloid leukemia receiving chemotherapy

**Authorization Guidelines:**

Approval of colony stimulating factors will be considered when prescribed by (or in consultation with) a hematologist or oncologist for a medically accepted indication/diagnosis when the drug and indication specific criteria are met.

Colony stimulating factors for non-FDA approved indications require medical literature/clinical studies from peer-reviewed journals with safety, efficacy and dosing information for the intended use.

**Chemotherapy-Induced Febrile Neutropenia: (Neupogen, Neulasta, Granix, Zarxio, and Leukine)**

- Patient is receiving chemotherapy for a NON-myeloid cancer (i.e., solid tumor, lymphoma)
  - For PRIMARY prophylaxis: Chemotherapy regimen has approximately ≥ 20% risk of febrile neutropenia OR member has risk factors for febrile neutropenia (e.g., age > 65, pre-existing neutropenia or tumor involvement in the bone marrow, infection, renal or liver impairment, other serious co-morbidities, advanced disease, HIV)
  - For SECONDARY prophylaxis: Patient previously experienced febrile neutropenia from the same chemotherapy regimen and reducing or delaying chemotherapy dose may compromise treatment outcome
  - For TREATMENT of febrile neutropenia in patients who did NOT receive CSF’s prophylaxis: Patient has risk factors for poor outcomes resulting from febrile neutropenia (e.g., age > 65, sepsis, severe neutropenia (ANC< 100/mcl), current infection, hospitalized at onset of fever, prior episode of febrile neutropenia)
- Administered 24 – 72 hours after completion of chemotherapy
- Patient is not receiving radiation therapy
- Chemotherapy cycle is given no more frequently than every 14 days (For Neulasta only)

**Severe chronic congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia: (Neupogen, Zarxio)**

- Patient has ONE of the following:
  - Evidence of inadequate bone marrow reserve (e.g., recurrent fevers, splenomegaly, mucosal ulcers, abdominal pain)
- High risk for developing serious bacterial infection (e.g., primarily severe neutropenia, indwelling venous catheters, prior serious infections)
- Current bacterial infection

**Neutropenia related to HIV: (Neupogen)**
- Patient has ONE of the following:
  - Evidence of inadequate bone marrow reserve (e.g., recurrent fevers, splenomegaly, mucosal ulcers, abdominal pain)
  - High risk for developing serious bacterial infection (e.g., primarily severe neutropenia, indwelling venous catheters, prior serious infections)
  - Patient has a documented bacterial infection
- Patient is taking antiretroviral therapy regimen that does NOT contain zidovudine
- Patient is NOT taking sulfamethaxazole/trimethoprim. NOTE: Patients who require pneumocystis prophylaxis should be switched to atovaquone or dapsone (unless contraindicated)

**Chemotherapy-induced neutropenia in acute myelogenous leukemia (AML): (Leukine)**
- Patient must be at least 55 years old
- Bone marrow is hypoplastic with < 5% blasts *(contraindicated in patients with excessive leukemic blasts (≥ 10%) in the bone marrow or peripheral blood)*
- Administered on day 11 (or 4 days after the completion) of induction therapy

**Neupogen and Zarxio may also be reviewed for medical necessity for treatment of the following indications:**
- Acute Myeloid Leukemia in patients receiving induction or consolidation chemotherapy
- Mobilization of hematopoietic progenitor cells before autologous stem cell transplant
- Mobilization of hematopoietic progenitor cells in the donor before allogenic stem cell transplant
- Treatment of acute radiation exposure, to increase survival, in patients who receive myelosuppressive doses of radiation at a dose of 2 gray (Gy)

**Leukine may also be reviewed for medical necessity for treatment of the following indications:**
- Bone marrow transplant failure or engraftment delay
- Myeloid reconstitution after allogenic bone marrow transplant
- Myeloid reconstitution after autologous bone marrow transplant in patients with Hodgkin’s disease, non-Hodgkin’s lymphoma, or acute lymphocytic leukemia
- Before and after autologous peripheral blood stem cell transplantation

**Non-FDA Approved Indications (e.g., MDS, HIV, aplastic anemia, drug-induced neutropenia):**
- Medical literature from peer-reviewed journals with safety, efficacy and dosing information for the intended use
- Recent ANC < 500 if used for treatment of neutropenia

**Initial Approval:**
- Chemotherapy-induced neutropenia (primary or secondary prophylaxis):
  - Approve per cycle of chemotherapy:
    - Up to a 14 day supply for Neupogen, Zarxio, Granix, and Leukine; one (1) 6 mg dose of Neulasta
    - Include refills if number of cycles is provided
Treatment of neutropenia (e.g., congenital, cyclic, or idiopathic, or after chemo + BMT):
  - Approve for 3 months

For off-label indications (e.g., myelodysplastic syndrome, HIV drug-induced neutropenia):
  - Short-term therapy: approve per cycle of chemotherapy, or 4 weeks at a time
  - Long-term therapy: approve x 6 months

**Renewal:**
- Chemotherapy-induced neutropenia (primary or secondary prophylaxis):
  - Recent ANC showing a response to therapy
  - Approve per cycle of chemotherapy:
    - Up to a 14 day supply for Neupogen, Zarxio, and Leukine; one (1) 6 mg dose of Neulasta
    - Include refills if number of cycles is provided
- All other indications:
  - Recent ANC
  - Recent platelet counts
  - Approve up to 1 year, depending on the indication

**Additional Information:**

*Note:* Neutropenia is defined as an absolute neutrophil count (ANC) less than 500, or an ANC of 1000 with an expected drop to <500 within the next 48 hours. ANC = % neutrophils x WBC.

Example: WBC 2.4, neutrophils 47% = 2400 x 0.47 = ANC 1128.

**Determining the risk of febrile neutropenia:**

A patient’s risk for developing neutropenic fever may be assessed prior to the use of colony stimulating factors. This may be achieved by evaluating the degree of myelosuppression of the patient’s chemotherapy regimen in addition to the presence of other patient-related risk factors. Both Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) recommend that colony stimulating factors be considered when the risk of febrile neutropenia is ≥20%.

**Chemotherapy regimen-related risk assessment:**

The aggressiveness of the chemotherapy regimen can be taken into account by giving to each individual drug a score (ranging from 0 to 4), according to its expected hematological toxicity. For combination drug regimens, the regimen’s score is calculated by taking the mean of the individual agent’s weights. (Example: vinblastine + carboplatin = 5 + 2 = 2.5). A score ≥3 is considered high risk for neutropenia. If the score is <3 it is considered lower risk and you should check for other risk factors before determining the final risk.

**Table 1: Individual scores of chemotherapy agents**

<table>
<thead>
<tr>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparaginase</td>
<td>6-Thioguanin</td>
<td>Actinomycin D</td>
<td>2-CDA</td>
<td>Adriamycin &gt;90 mg/m²</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>5-fluorouracil</td>
<td>Dacarbazine</td>
<td>Adriamycin ≤90 mg/m²</td>
<td>Busulfan</td>
</tr>
<tr>
<td>Farnesyl</td>
<td>Cisplatin</td>
<td>Fludarabin</td>
<td>Alimta</td>
<td>Carmustine</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Gemcitabine</td>
<td>Mechloretamine</td>
<td>Amsacrin</td>
<td>Cyclophosphamide &gt;1 g/m²</td>
</tr>
<tr>
<td>Methotrexate + leucovorin</td>
<td>Chlorambucil</td>
<td>Melphalan ≤70 mg/m²</td>
<td>Bendamustin</td>
<td>Cytarabin (Ara C) &gt;2 g/m²</td>
</tr>
</tbody>
</table>
### Score Calculator

**Score 0**
- STI 571
- Thalidomide
- Tretinoide
- Bortezomib
- Vincristine
- Campath

**Score 1**
- Vindesine
- Mitoxantrone
- Purinethol
- Hydroxyurea
- Temozolomide
- Vinblastine

**Score 2**
- Mitomycin C
- Carboplatin
- Cytarabine (Ara C)
- Daunorubicin
- Etoposide

**Score 3**
- Camptothecin
- Procarbazine
- Epirubicin
- Ifosfamide > 9 g/m²
- Teniposide

**Score 4**
- Docetaxel
- Etoposide > 100 mg/m²
- Gemtuzumab
- Idarubicin
- Topotecan
- Oxaliplatin
- Teniposide

A weight (0–4) is assigned to each drug according to its expected frequency of severe neutropenia (0 unusual, 1 very rare, 2 rare, 3 frequent, 4 very frequent). This weight was determined using data on the basis of single drug therapy.


### Patient-related risk factors:

- In addition to the risk of chemotherapy regimen, these factors need to be considered when evaluating a patient’s overall risk
  - Age ≥ 65 years old
  - Previous chemotherapy or radiation therapy
  - Preexisting neutropenia or bone marrow involvement with tumor
  - Preexisting conditions
    - Neutropenia
    - Infection/open wounds
    - Recent surgery
  - Poor performance status
  - Poor renal function
  - Liver dysfunction (most notably elevated bilirubin)
  - HIV-infected patient (in particular, patients with low CD4 counts)

- **MASCC Score Calculator** [Click here to open the calculator]
  - Score < 21 indicates a patient is at high risk of febrile neutropenia complications

### References:


