Subject: Colony Stimulating Factors
- Neupogen® (Filgrastim)
- Granix™ (tbo-filgrastim)
- Neulasta® (Pegfilgrastim)
- Leukine® (Sargramostim)
- Zarxio™ (filgrastim-sndz)

Prior approval is required for some or all procedure codes listed in this Corporate Medical Policy.

Definition: Colony stimulating factors (e.g., Neupogen, Granix, Neulasta, Leukine, Zarxio) are recombinant cytokine proteins that act on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment and end cell functional activation. These glycoproteins stimulate bone marrow proliferation, reduce the maturation time of neutrophils, increase peripheral neutrophil count and prevent infection.

The site of care medical necessity criteria applies to initial therapy and reauthorizations.

I. Granix:

Medical Necessity: The Company considers Granix (HCPCS Code J1447) medically necessary and eligible for reimbursement providing that at least one of the following medical criteria is met:

- Prevention of febrile neutropenia (FN) in those receiving myelosuppressive chemotherapy AND one of the following:
  - The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
  - 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
  - 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]).
injection]) and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
  o 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).

AND

• Granix will not be taken in combination with another colony stimulating factor (e.g., Neupogen, Neulasta, Leukine, Zarxio); AND
• Medication is prescribed by, or in consultation with, an oncologist, radiologist, radiation oncologist, physician with expertise in treating acute radiation injury, hematologist, transplantation specialist, infection disease specialist or HIV/AIDS specialist; AND
• Dosage and administration are consistent with the U.S. Food and Drug Administration approved label:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of neutropenia in those receiving myelosuppressive chemotherapy</td>
<td>5 mcg/kg per day administered subcutaneously. Daily dosing with Granix should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range</td>
</tr>
</tbody>
</table>

AND

• Site of care medical necessity is met*.

II. Leukine:

Medical Necessity: The Company considers Leukine (HCPCS Code J2820) medically necessary and eligible for reimbursement providing that at least one of the following medical criteria is met:

• Used following induction chemotherapy in Acute Myelogenous Leukemia (AML); OR
• Prevention of febrile neutropenia (FN) in AML; OR
• Adjunctive therapy for bone marrow transplant; OR
• Myelodysplasia therapy; OR
• Radiation injury (syndrome); OR
• For mobilization/transplantation of peripheral blood progenitor cells (harvesting of blood stem cells)

This document is subject to the disclaimer found at http://www.medmutual.com/provider/MedPolicies/Disclaimer.aspx. If printed, this document is subject to change. Always verify with the most current version of the official document at http://www.medmutual.com/provider/MedPolicies/Disclaimer.aspx.
Leukine will not be taken in combination with another colony stimulating factor (e.g., Neupogen, Granix, Neulasta, Zarxio); and

Medication prescribed by, or in consultation with, an oncologist, radiologist, radiation oncologist, physician with expertise in treating acute radiation injury, hematologist, transplantation specialist, infection disease specialist or HIV/AIDS specialist; and

Dosage and administration are consistent with the U.S. Food and Drug Administration approved label:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil recovery following chemotherapy in acute myelogenous leukemia</td>
<td>250 mcg/m²/day administered intravenously over a four hour period starting approximately on day 11 or four days following the completion of induction chemotherapy, if the day 10 bone marrow is hypoplastic with &lt;5% blasts. If a second cycle of induction chemotherapy is necessary, Leukine should be administered approximately four days after the completion of chemotherapy if the bone marrow is hypoplastic with &lt;5% blasts. Leukine should be continued until an ANC &gt;1500 cells/mm³ for three consecutive days or a maximum of 42 days.</td>
</tr>
<tr>
<td>Mobilization of peripheral blood progenitor cells</td>
<td>250 mcg/m²/day administered intravenously over 24 hours or subcutaneous once daily. Dosing should continue at the same dose through the period of peripheral blood progenitor cell collection.</td>
</tr>
<tr>
<td>Post peripheral blood progenitor cell transplantation</td>
<td>250 mcg/m²/day administered intravenously over 24 hours or subcutaneous once daily beginning immediately following infusion of progenitor cells and continuing until an ANC&gt;1500 cells/mm³ for three consecutive days is attained.</td>
</tr>
<tr>
<td>Myeloid reconstitution after autologous or allogeneic bone marrow transplantation</td>
<td>250 mcg/m²/day administered intravenously over a two-hour period beginning two to four hours after bone marrow infusion, and not less than 24 hours after the last dose of chemotherapy or radiotherapy. Leukine should be continued until an ANC &gt;1500 cells/mm³ for three consecutive days is attained.</td>
</tr>
<tr>
<td>Bone marrow transplantation failure or engraftment delay</td>
<td>250 mcg/m²/day for 14 days as a 2-hour IV infusion. The dose can be repeated after seven days of therapy if engraftment has not occurred. If engraftment still has not occurred, a third course of 500 mcg/m²/day for 14 days may be tried after another seven days off therapy. If there is still no improvement, it is unlikely that further dose escalation will be beneficial.</td>
</tr>
</tbody>
</table>

Site of care medical necessity is met*.

* Site of care medical necessity is met*.
III. Neulasta:

Medical Necessity: The Company considers Neulasta (HCPCS Code J2505) medically necessary and eligible for reimbursement providing that at least one of the following medical criteria is met:

- Neutropenia due to radiation injury (syndrome); OR
- Prevention of febrile neutropenia (FN) in those receiving myelosuppressive chemotherapy and one of the following is met:
  - The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
  - 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
  - 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, Zalexio™, [filgrastim-sndz injection], Granix® [tbo-filgrastim injection]) and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
- Mobilization peripheral blood progenitor cell transplantation (harvesting);

AND

- Neulasta will not be taken in combination with another colony stimulating factor (e.g., Neupogen, Granix, Leukine, Zalexio); and
- Medication prescribed by, or in consultation with, an oncologist, radiologist, radiation oncologist, physician with expertise in treating acute radiation injury, hematologist, transplantation specialist, infection disease specialist or an HIV/AIDS specialist; and
- Dosage and administration are consistent with the U.S. Food and Drug Administration approved label:
<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Cancer Receiving Myelosuppressive Chemotherapy</td>
<td>Adults: 6 mg administered subcutaneously once per chemotherapy cycle. Infants, children and adolescents &lt;45 kg: weight based (refer to package insert) once per chemotherapy cycle; maximum dose is 6 mg</td>
</tr>
<tr>
<td>Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome</td>
<td>Adults: two doses, 6 mg each, administered subcutaneously one week apart &lt;45 kg: weight based (refer to package insert)</td>
</tr>
</tbody>
</table>

AND

- Site of care medical necessity is met*.

IV. Neupogen:

Medical Necessity: The Company considers Neupogen (HCPCS Code J1442) medically necessary and eligible for reimbursement providing that at least one of the following medical criteria is met:

- Neutropenia due to adjunctive therapy for bone marrow transplant; OR
- Neutropenia due to HIV/AIDS or HIV/AIDS-related drug therapy; OR
- Neutropenia due to drug therapy or radiation (agranulocytosis); OR
- Severe chronic neutropenia (e.g., cyclic neutropenia); OR
- Myelodysplasia therapy; OR
- Aplastic anemia; OR
- Radiation injury (syndrome); OR
- Patients with Acute Myeloid Leukemia receiving induction or consolidation chemotherapy; OR
- For mobilization/transplantation of peripheral blood progenitor cells (harvesting); OR
- Prevention of febrile neutropenia (FN) in those receiving myelosuppressive chemotherapy and one of the following is met:
  - The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
  - 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
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], Granix® [tbo-filgrastim injection]) and a reduced dose or frequency of chemotherapy may compromise treatment outcome;

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).

AND

- Neupogen will not be taken in combination with another colony stimulating factor (e.g., Granix, Neulasta, Leukine, Zarxio); and
- Medication is prescribed by, or in consultation with, an oncologist, radiologist, radiation oncologist, physician with expertise in treating acute radiation injury, hematologist, transplantation specialist, infection disease specialist or HIV/AIDS specialist; and
- Dosage and administration are consistent with the U.S. Food and Drug Administration approved label:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer patients receiving myelosuppressive chemotherapy</td>
<td>5 mcg/kg/day, administered as a single daily injection by subcutaneous bolus injection, by short intravenous infusion (15 to 30 minutes) or by continuous subcutaneous or continuous intravenous infusion. Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir. Neupogen should be administered daily for up to two weeks, until the ANC is ≥10,000/mm³ following the expected chemotherapy-induced neutrophil nadir. The duration of Neupogen therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Neupogen therapy should be discontinued if the ANC surpasses 10,000/mm³ after the expected chemotherapy-induced neutrophil nadir. In phase 3 trials, efficacy was observed at doses of 4-8 mcg/kg/day.</td>
</tr>
</tbody>
</table>
| Cancer patients receiving bone marrow transplant | 10 mcg/kg/day given as an intravenous infusion of four or 24 hours, or as a continuous 24-hour subcutaneous infusion. During the period of neutrophil recovery, the daily dose of Neupogen should be titrated against the neutrophil response as follows:  
  - When ANC >1000/mm³ for three consecutive days, reduce to 5 mcg/kg/day*  
  - Then, if ANC remains >1000/mm³ for three more consecutive days, discontinue Neupogen |
Peripheral blood progenitor cell collection

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mcg/kg/day subcutaneously, either as a bolus or continuous infusion. Neupogen is recommended to be given for at least four days before the first leukapheresis procedure and continued until the last leukapheresis. Although the optimal duration of Neupogen administration and leukapheresis schedule have not been established, administration of Neupogen for 6-7 days with leukapheresis on days 5, 6 and 7 was found to be safe and effective.</td>
<td></td>
</tr>
</tbody>
</table>

Severe chronic neutropenia:

- **Congenital neutropenia**
  - **Starting dose:** 6 mcg/kg twice a day subcutaneously every day.
  - **Dose adjustments:** Chronic daily administration is required to maintain clinical benefit. Absolute neutrophil count should not be used as the sole indication of efficacy. The dose should be individually adjusted based on the patient’s clinical course as well as ANC.

- **Idiopathic or cyclic neutropenia**
  - **Starting dose:** 5 mcg/kg as a single injection subcutaneously every day.
  - **Dose adjustments:** Chronic daily administration is required to maintain clinical benefit. Absolute neutrophil count should not be used as the sole indication of efficacy. The dose should be individually adjusted based on the patient’s clinical course as well as ANC.

Cancer patients receiving myelosuppressive radiation

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mcg/kg as a single daily subcutaneous injection for patients exposed to myelosuppressive doses of radiation. Administer Neupogen as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).</td>
<td></td>
</tr>
</tbody>
</table>

**AND**

- Site of care medical necessity is met*.

V. Zarxio:

**Medical Necessity:** The Company considers Zarxio (HCPCS Code Q5101) medically necessary and eligible for reimbursement providing that **at least one** of the following medical criteria is met:

- Neutropenia due to adjunctive therapy for bone marrow transplant; OR
- Neutropenia due to HIV/AIDS or HIV/AIDS-related drug therapy; OR
- Neutropenia due to drug therapy or radiation (agranulocytosis); OR
- Severe chronic neutropenia (e.g., cyclic neutropenia); OR
- Myelodyplasia therapy; OR
- Aplastic anemia; OR
• Radiation injury (syndrome); OR
• Patients with Acute Myeloid Leukemia receiving induction or consolidation chemotherapy; OR
• For mobilization/transplantation of peripheral blood progenitor cells (harvesting); OR
• Prevention of febrile neutropenia (FN) in those receiving myelosuppressive chemotherapy and one of the following is met:
  o The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
  o 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
  o 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], Granix® [tbo-filgrastim injection]) and a reduced dose or frequency of chemotherapy may compromise treatment outcome;
  o 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).

AND

• Zarxio will not be taken in combination with another colony stimulating factor (e.g., Granix, Neupogen, Neulasta, Leukine); and
• Medication is prescribed by, or in consultation with, an oncologist, radiologist, radiation oncologist, physician with expertise in treating acute radiation injury, hematologist, transplantation specialist, infection disease specialist or HIV/AIDS specialist; and
• Dosage and administration are consistent with the U.S. Food and Drug Administration approved label:
### Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer patients receiving myelosuppressive chemotherapy</td>
<td><em>5 mcg/kg/day, administered as a single daily injection by subcutaneous bolus injection, by short intravenous infusion (15 to 30 minutes) or by continuous subcutaneous or continuous intravenous infusion. Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir. Zarxio should be administered daily for up to two weeks, until the ANC is ≥10,000/mm³ following the expected chemotherapy-induced neutrophil nadir. The duration of Zarxio therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Zarxio therapy should be discontinued if the ANC surpasses 10,000/mm³ after the expected chemotherapy-induced neutrophil nadir.</em></td>
</tr>
</tbody>
</table>
| Cancer patients receiving bone marrow transplant                            | *10 mcg/kg/day given as an intravenous infusion of four or 24 hours, or as a continuous 24-hour subcutaneous infusion. During the period of neutrophil recovery, the daily dose of Zarxio should be titrated against the neutrophil response as follows:*  
  - When ANC >1000/mm³ for three consecutive days, reduce to 5 mcg/kg/day*  
  - Then, if ANC remains >1000/mm³ for three more consecutive days, discontinue Zarxio  
  - Then, if ANC decreases to <1000/mm³, resume at 5 mcg/kg/day  
  
  *If ANC decreases to <1000/mm³ at any time during the 5 mcg/kg/day administration, Zarxio should be increased to 10 mcg/kg/day, and the above steps should then be followed.** |
| Peripheral blood progenitor cell collection and therapy in cancer patients   | *10 mcg/kg/day subcutaneously, either as a bolus or continuous infusion. Zarxio is recommended to be given for at least four days before the first leukapheresis procedure and continued until the last leukapheresis. Although the optimal duration of Zarxio administration and leukapheresis schedule have not been established, administration of Zarxio for 6-7 days with leukapheresis on days 5, 6 and 7 was found to be safe and effective.* |
| Severe chronic neutropenia:                                                 | **Starting dose:** 6 mcg/kg twice a day subcutaneously every day. **Dose adjustments:** Chronic daily administration is required to maintain clinical benefit. Absolute neutrophil count should not be used as the sole indication of efficacy. The dose should be individually adjusted based on the patient’s clinical course as well as ANC. |
| • Congenital neutropenia                                                    | **Starting dose:** 5 mcg/kg as a single injection subcutaneously every day. **Dose adjustments:** Chronic daily administration is required to maintain clinical benefit. Absolute neutrophil count should not be used as the sole indication of efficacy. The dose should be individually adjusted based on the patient’s clinical course as well as ANC. |
| • Idiopathic or cyclic neutropenia                                          | **AND**                                                                                                                                                    |
• Site of care medical necessity is met*.

* MMO Site of Care Medical Necessity Criteria:

• Medications in this policy will be administered or billed with a place of service that identifies the location to be a non-hospital facility based location (i.e., home infusion provider, provider’s office, free-standing ambulatory infusion center) unless at least one of the following are met†:

1. Age <21 years; or
2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
3. History of a severe adverse event from previous administration of the prescribed medication; or
4. Requested medication is being administered as follows:
   • part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
   • administered with dialysis; or
5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
6. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

No initial doses are allowed in a hospital based outpatient facility without other above criteria being met.

†This criterion does not apply to Medicare or Medicare Advantage members.

Sources of Information:

• Granix™ injection [prescribing information]. North Wales, PA: Teva Pharmaceuticals; December 2014.
• Zarfot® injection for subcutaneous or intravenous use [prescribing information]. Princeton, NJ: Sandoz; August 2015.
Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

Prior approval is required for HCPCS Codes J1442, J1447, J2505, J2820 and Q5101.