Clinical Policy: Filgrastim (Neupogen), Filgrastim-sndz (Zarxio), Tbo-filgrastim (Granix)
Reference Number: ERX.SPA.58
Effective Date: 09.01.17
Last Review Date: 08.18

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Filgrastim (Neupogen®) and its biosimilars, filgrastim-sndz (Zarxio®) and tbo-filgrastim (Granix®), are human granulocyte colony-stimulating factors.

FDA Approved Indication(s)
Granix is indicated for reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN).

Neupogen and Zarxio are indicated to:
• Decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever
• Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
• Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., FN, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)
• Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
• Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

Neupogen is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Granix, Neupogen, and Zarxio are medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Chemotherapy-Induced Neutropenia (must meet all):
      1. Diagnosis of non-myeloid malignancy or AML;
      2. Prescribed for use following myelosuppressive chemotherapy;
      3. For Zarxio or Granix requests, failure of Neupogen*, unless contraindicated or clinically significant adverse effects are experienced;
      4. Dose does not exceed 30 mcg/kg/day [IV] or 24 mcg/kg/day [SC].
      Approval duration: 6 months
   
   B. Bone Marrow Transplantation (must meet all):
      1. Diagnosis of non-myeloid malignancy;
      2. Member is undergoing myeloablative chemotherapy following BMT;
3. For Zarxio or Granix requests, failure of Neupogen*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization is (or may be) required for Neupogen
4. Dose does not exceed 10 mcg/kg/day.
   Approval duration: 6 months

C. Peripheral Blood Progenitor Cell Collection (must meet all):
1. Prescribed for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis;
2. The prescribed drug will be initiated before leukapheresis (e.g., prescribed for 6 to 7 days with leukapheresis on days 5, 6, and 7);
3. For Zarxio or Granix requests, failure of Neupogen*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization is (or may be) required for Neupogen
4. Dose does not exceed 10 mcg/kg/day.
   Approval duration: 1 month

D. Chronic Neutropenia (must meet all):
1. Prescribed for use in symptomatic (e.g., fever, infections, oropharyngeal ulcers) severe chronic neutropenia caused by congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia;
2. For Zarxio or Granix requests, failure of Neupogen*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization is (or may be) required for Neupogen
3. Dose does not exceed: 30 mcg/kg/day [IV] or 24 mcg/kg/day [SC].
   Approval duration: 6 months

E. Acute Radiation Syndrome (must meet all):
1. Prescribed for use following suspected or confirmed acute exposure to myelosuppressive doses of radiation;
2. For Zarxio or Granix requests, failure of Neupogen*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization is (or may be) required for Neupogen
3. Dose does not exceed 10 mcg/kg/day.
   Approval duration: 6 months

F. Myelodysplastic Syndrome (off-label) (must meet all):
1. Diagnosis of myelodysplastic syndrome with symptomatic anemia without del (5q) abnormality,
2. Current (within the past 30 days) serum erythropoietin level ≤ 500 mU/mL;
3. For Zarxio or Granix requests, failure of Neupogen*, unless contraindicated or clinically significant adverse effects are experienced;
   *Prior authorization is (or may be) required for Neupogen
4. Request meets one of the following (a or b):
   a. Dose does not exceed 5 mcg/kg/day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   Approved duration: 6 months

G. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
A. All Indications in Section I (must meet all):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Dose does not exceed the FDA-approved maximum recommended dose for the relevant indication.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information
Appendix A: Abbreviation/Acronym Key
AML: acute myeloid/myelogenous leukemia
ANC: absolute neutrophil count
BMT: bone marrow transplantation
FDA: Food and Drug Administration
FN: febrile neutropenia
G-CSF: granulocyte colony-stimulating factor

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications
Not applicable

Appendix D: General Information
- Zarxio is not recommended in patients requiring direct administration of less than 0.3 mL due to the potential for dosing errors. The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of Zarxio less than 0.3 mL (180 mcg).
- Neutropenia is defined as an absolute neutrophil count (ANC) of < 500 neutrophils/mcL or an ANC of < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours. Neutropenia can progress to FN, defined as a single temperature of ≥ 38.8°C orally or ≥ 38.0°C over 1 hour.
- The development of febrile neutropenia is a common dose-limiting toxicity of many chemotherapy regimens. This risk is directly related to the intensity of the chemotherapy regimen. Chemotherapy regimens that have an incidence of febrile neutropenia greater than 20% in clinical trials in chemotherapy naïve patients are considered by the National Comprehensive Cancer Network (NCCN) panel at high risk. Prophylaxis with myeloid growth factors is recommended at this level of risk (Category 1 recommendation). NCCN Compendium recommend prophylaxis be considered in intermediate-risk (10-20% overall risk of FN) patients (Category 2A recommendation). In addition to chemotherapy regimens, other risk factors such as: treatment-related, patient related, cancer-related, and co-morbidities have also been associated with an increased risk of febrile neutropenia. Therefore, the type of chemotherapy regimen is only one component of the risk assessment.
- For chemotherapy patients, continuing filgrastim until the ANC has reached 10,000/mm³ following the expected chemotherapy-induced neutrophil nadir (as specified in the G-CSF package insert), is known to be safe and effective. However, a shorter duration of administration that is sufficient
to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost.

- Evidence supports dose reduction of pegylated interferon according to FDA-approved labeling as treatment for neutropenia occurring in hepatitis C patients treated with combination therapy (pegylated interferon + ribavirin). Treatment with filgrastim is not FDA approved or recommended by current hepatitis C treatment guidelines except in patients with decompensated cirrhosis.

- There are insufficient data to support the use of filgrastim to treat febrile neutropenia in patients who have received prophylactic Neulasta.

- In a randomized, double-blind, multi-center safety and efficacy study of 218 breast cancer patients receiving chemotherapy with a high risk of neutropenia, Zarxio was non-inferior to Neupogen on the primary endpoint of duration of severe neutropenia (1.17 days for Zarxio and 1.20 days for Neupogen).

- NCCN guidelines for myelodysplastic syndrome list filgrastim with a category 2A recommendation for use as initial treatment of symptomatic anemia in lower risk disease with no del (5q), serum erythropoietin levels ≤500 mU/mL, and ring sideroblasts ≥15%. Filgrastim may also be considered for the treatment of symptomatic anemia in lower risk disease with serum erythropoietin levels ≤500 mU/mL, and ring sideroblasts <15% when there is no response to epoetin or darbepoetin alone (category 2A recommendation).

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim (Neupogen), filgrastim-sndz (Zarxio)</td>
<td>Chemotherapy-induced neutropenia</td>
<td>5 mcg/kg SC or IV QD</td>
<td>30 mcg/kg/day [IV] or 24 mcg/kg/day [SC]</td>
</tr>
<tr>
<td>Chronic neutropenia</td>
<td>Congenital: 6 mcg/kg SC BID</td>
<td>30 mcg/kg/day [IV] or 24 mcg/kg/day [SC]</td>
<td></td>
</tr>
<tr>
<td>Idiopathic or cyclic: 5 mcg/kg SC QD</td>
<td>Do not administer 24 hours before and after chemotherapy</td>
<td></td>
<td></td>
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<tr>
<td>BMT</td>
<td>10 mcg/kg IV or SC infusion QD</td>
<td>10 mcg/kg/day</td>
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<tr>
<td>Peripheral blood progenitor cell collection</td>
<td>10 mcg/kg SC bolus or continuous infusion QD</td>
<td>10 mcg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Patients acutely exposed to myelosuppressive doses of radiation</td>
<td>10 mcg/kg SC QD</td>
<td>10 mcg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Tbo-filgrastim (Granix)</td>
<td>Myelosuppressive chemotherapy</td>
<td>5 mcg/kg SC or IV QD</td>
<td>5 mcg/kg/day</td>
</tr>
</tbody>
</table>

VI. Product Availability

<table>
<thead>
<tr>
<th>Drug</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim (Neupogen)</td>
<td>Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL Single-dose vials for injection: 300 mg/mL, 480 mg/1.6 mL</td>
</tr>
<tr>
<td>Filgrastim-sndz (Zarxio)</td>
<td>Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL</td>
</tr>
<tr>
<td>Tbo-filgrastim (Granix)</td>
<td>Single-dose prefilled syringes for injection: 300 mcg/0.5 mL, 480 mcg/0.8 mL</td>
</tr>
</tbody>
</table>
VII. References

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy split from ERX.SPMN.07 Colony Stimulating Factors and converted to new template. Renewal criteria added. Separated criteria by indication rather than by drug. All off-label uses are referred to the off-label use policy. Changed approval duration for peripheral blood progenitor cell collection and for acute radiation syndrome to reflect actual duration of therapy for these indications. Removed requirements to avoid administration within a certain timeframe of administering chemotherapy.</td>
<td>07.17</td>
<td>08.17</td>
</tr>
<tr>
<td>3Q 2018 annual review: allowed Granix for all indications covered by Neupogen or Zarxio; revised max dosing for chemotherapy-induced neutropenia and chronic neutropenia per Clinical Pharmacology; removed radiation exposure requirement; added off-label use in myelodysplastic syndrome per NCCN Compendium; references reviewed and updated.</td>
<td>05.02.18</td>
<td>08.18</td>
</tr>
</tbody>
</table>

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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