Granulocyte Colony-Stimulating Factor (G-CSF) Use in Adult Patients

Effective Date: Feb. 1, 2020
Last Revised: Jan. 9, 2020
Replaces: N/A

RELATED MEDICAL POLICIES:
None

Introduction

People with certain cancers may be given drugs (chemotherapy) to treat their disease. A side effect of many chemotherapy drugs is destruction of or delay in making immune cells that fight infection. These cells are known as white blood cells, neutrophils, or granulocytes. Neutropenia means a lack of granulocytes (infection-fighting cells). People being treated for cancer may develop neutropenia and fever. When this happens, treatment with antibiotics in the hospital is often necessary in case there is a serious infection. In the 1980s scientists discovered a type of protein called granulocyte-colony stimulating factor (G-CSF) that stimulates the body to make more granulocytes. It has become a standard practice to give G-CSF drugs along with certain types of chemotherapy likely to cause neutropenia. These agents can also be given as part of a bone marrow or stem cell transplant or to treat some rare conditions. Recently new forms of these agents, which are less costly, have become available; studies show them to be equivalent. The newer agents, Granix® (tbo-filgrastim) and Nivestym™ (filgrastim-aafi) are less costly and therefore are preferred for coverage. Granix® and Nivestym™ do not need preapproval for coverage. All other G-CSF agents require preapproval. Depending on the diagnosis, using Granix® or Nivestym™ may be necessary before one of the other drugs is covered.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
**Policy Coverage Criteria**

This policy applies to patients aged **18 years and over**.

<table>
<thead>
<tr>
<th>Targeted Use</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Patients treated with myelosuppressive anti-cancer regimens, at risk of severe febrile neutropenia** to decrease the incidence of infection | Granix® (tbo-filgrastim) or Nivestym™ (filgrastim-aafi) may be considered medically necessary as first-line therapy for adult and pediatric patients. Granix® (tbo-filgrastim) and Nivestym™ (filgrastim-aafi) do not need preapproval for coverage. Neupogen® (filgrastim), Zarxio® (filgrastim-sndz), Neulasta® (pegfilgrastim) / Neulasta Onpro®, Fulphila™ (pegfilgrastim-jmdb), Udenyca™ (pegfilgrastim-cbqv), or Ziextenzo™ (pegfilgrastim-bmez) may be considered medically necessary for:  
  • Treatment of patients less than 18 years of age OR  
  • Treatment of adults as second-line therapy when documentation for one of the following is provided:  
    o Granix® (tbo-filgrastim) or Nivestym™ (filgrastim-aafi) has been tried and failed OR  
    o There is a contraindication to the use of Granix® (tbo-filgrastim) and Nivestym™ (filgrastim-aafi) OR  
    o A valid medical rationale is provided for why self-injection or home nursing cannot be performed |

**For purposes of this policy, the following types of patients are considered to be at risk of severe febrile neutropenia:**

1. Patients that have experienced febrile neutropenia during a previous cycle of treatment with the current chemotherapy regimen OR
<table>
<thead>
<tr>
<th>Targeted Use</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Patients receiving chemotherapy regimen that is expected to result in a</td>
<td>2. Patients receiving chemotherapy regimen that is expected to result in a 20% or higher incidence of FN, based on guidelines from the American Society of Clinical Oncology (see Appendix, Smith et al, 2006)</td>
</tr>
<tr>
<td>3. Patients with bone marrow impairment</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>4. Patients that have received 2 or more prior chemotherapy regimens or</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>extensive radiation</td>
<td>5. Patients with other serious comorbidities (reviewed on a case basis)</td>
</tr>
<tr>
<td><strong>Note:</strong> Colony-stimulating factors should not be routinely used for afebrile neutropenia (Smith et al, 2006).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients undergoing autologous peripheral blood progenitor cell collection and therapy</th>
<th>Nivestym™ (filgrastim-aafi) may be considered medically necessary as first-line therapy for adult and pediatric patients. Nivestym™ (filgrastim-aafi) does not need preapproval for coverage.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupogen® (filgrastim) and Zarxio® (filgrastim-sndz) may be considered medically</td>
<td><strong>Neupogen® (filgrastim) and Zarxio® (filgrastim-sndz) may be considered medically necessary for:</strong></td>
</tr>
<tr>
<td>necessary for:</td>
<td>• Treatment of patients less than 18 years of age</td>
</tr>
<tr>
<td>OR</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>• Treatment of adults as second-line therapy when documentation for one of the</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>following is provided:</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>o Nivestym™ (filgrastim-aafi) has been tried and failed</td>
<td>o There is a contraindication to the use of Nivestym™ (filgrastim-aafi)</td>
</tr>
<tr>
<td>OR</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>o A valid medical rationale is provided for why self-injection or home nursing</td>
<td>o A valid medical rationale is provided for why self-injection or home nursing cannot be performed</td>
</tr>
<tr>
<td>cannot be performed</td>
<td></td>
</tr>
</tbody>
</table>

<p>| Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic)      | Neupogen® (filgrastim) and Neulasta® (pegfilgrastim) / Neulasta Onpro® may be considered medically necessary as first-line therapy for adult and pediatric patients.                                                                 |</p>
<table>
<thead>
<tr>
<th>Targeted Use</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsyndrome of Acute Radiation Syndrome)</td>
<td>Neulasta® (pegfilgrastim) / Neulasta Onpro®, Fulphila™ (pegfilgrastim-jmdb), Udenyca™ (pegfilgrastim-cbqv), or Ziextenzo™ (pegfilgrastim-bmez) may be considered medically necessary as first-line therapy when used in combination with chemotherapy regimens where pegfilgrastim was the only G-CSF product used in published clinical trials.</td>
</tr>
<tr>
<td>Combination treatment with chemotherapy regimens</td>
<td>• When using Neulasta® (pegfilgrastim) / Neulasta Onpro®, Fulphila™ (pegfilgrastim-jmdb), Udenyca™ (pegfilgrastim-cbqv), or Ziextenzo™ (pegfilgrastim-bmez) for this reason, the requesting provider should provide article citations supporting the request.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targeted Use</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not listed in this policy</td>
<td>Any other uses of the following G-CSF products not addressed in this policy are considered investigational:</td>
</tr>
<tr>
<td></td>
<td>• Fulphila™ (pegfilgrastim-jmdb)</td>
</tr>
<tr>
<td></td>
<td>• Granix® (tbo-filgrastim)</td>
</tr>
<tr>
<td></td>
<td>• Neulasta® (pegfilgrastim) / Neulasta Onpro®</td>
</tr>
<tr>
<td></td>
<td>• Neupogen® (filgrastim)</td>
</tr>
<tr>
<td></td>
<td>• Nivestym™ (filgrastim-aafi)</td>
</tr>
<tr>
<td></td>
<td>• Udenyca™ (pegfilgrastim-cbqv)</td>
</tr>
<tr>
<td></td>
<td>• Zarxio® (Filgrastim-sndz)</td>
</tr>
<tr>
<td></td>
<td>• Ziextenzo™ (pegfilgrastim-bmez)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>Drugs listed in policy may be approved up to 12 months.</td>
</tr>
<tr>
<td>Initial authorization</td>
<td></td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Future re-authorization may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the patient continues to show a positive clinical response to therapy.</td>
</tr>
</tbody>
</table>
Documentation Requirements

The patient's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, targeted use of G-CSF product, relevant history, physical evaluation and medication history

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Application of on-body injector (includes cannula insertion) for timed subcutaneous injection (Neulasta Onpro®) (Both injector and drug are inclusive)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J1442 Injection, filgrastim (G-CSF) (Neupogen®), 1 microgram</td>
</tr>
<tr>
<td></td>
<td>J1447 Injection, tbo-filgrastim (Granix®), 1 microgram</td>
</tr>
<tr>
<td></td>
<td>J2505 Injection, pegfilgrastim (Neulasta®), 6 mg</td>
</tr>
<tr>
<td></td>
<td>J3590 Unclassified biologics (use to report Ziextenzo™ only)</td>
</tr>
<tr>
<td></td>
<td>Q5101 Injection, filgrastim-sndz, biosimilar, (Zarxio®), 1 microgram</td>
</tr>
<tr>
<td></td>
<td>Q5108 Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila™), 0.5 mg</td>
</tr>
<tr>
<td></td>
<td>Q5110 Injection, filgrastim-aafi, biosimilar, (Nivestym™), 1 microgram</td>
</tr>
<tr>
<td></td>
<td>Q5111 Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca™), 0.5 mg</td>
</tr>
</tbody>
</table>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

This policy addresses the following granulocyte colony-stimulating factors:
Granix® (tbo-filgrastim)

A non-glycosylated recombinant methionyl human granulocyte colony-stimulating growth factor (r-metHuG-CSF) manufactured by recombinant DNA technology using the bacterium strain E coli K802. It is identical in amino acid sequence to filgrastim but is produced by a different manufacturer using a slightly different process. Granix® (tbo-filgrastim) was reviewed by the FDA independent of the original BLA for filgrastim and was assigned the prefix “Tbo” to differentiate the two. Both are produced in vitro using genetically engineered strains of E. coli. Granix® (tbo-filgrastim) is indicated to reduce 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 because it was independently labelled as a separate drug by FDA it has slightly different labelled indications from Neupogen, however, it has identical labelling and indications for FN.

Nivestym® (filgrastim-aafi)

Nivestym® (filgrastim-aafi) is a biosimilar to Neupogen® (filgrastim). Filgrastim-aafi is a 175 amino acid human G-CSF manufactured by recombinant DNA technology. Nivestym® is produced by E coli bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E coli. Because Nivestym® is produced in E coli, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

Neupogen® (filgrastim)

A recombinant human granulocyte colony-stimulating factor produced by Amgen, Inc. It is recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF, which is a 175 amino acid protein identical to the endogenous growth factor except for an inserted N-terminal methionine and the lack of glycosylation). Neupogen® (filgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs in one of the following categories:

1. Cancer patients receiving myelosuppressive chemotherapy
2. Patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy

3. Cancer patients receiving bone marrow transplantation

4. Patients undergoing Peripheral Blood Progenitor Cell Collection and Therapy

5. Patients with Severe Chronic Neutropenia

Patients in these categories are associated with a significant incidence of severe febrile neutropenia (FN).

**Zarxio® (filgrastim-sndz)**

A 175 amino acid human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology. Zarxio® (filgrastim-sndz) is produced by Escherichia coli (E coli) bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. Zarxio has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E coli. Because Zarxio is produced in E coli, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

**Neulasta® (pegfilgrastim) / Neulasta Onpro®**

A covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Neulasta® (pegfilgrastim) / Neulasta Onpro® is indicated to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia.

**Fulphila® (pegfilgrastim-jmdb)**

Fulphila® (pegfilgrastim-jmdb) is a biosimilar to Neulasta® (pegfilgrastim). Pegfilgrastim-jmdb is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a
strain of E coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim-jmdb a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF.

Udenyca™ (pegfilgrastim-cbqv)

Udenyca™ (pegfilgrastim-cbqv) is a biosimilar to Neulasta® (pegfilgrastim). Pegfilgrastim-cbqv is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a strain of E coli transformed with a genetically engineered plasmid containing the human G-CSF gene. During the pegfilgrastim-cbqv manufacturing process, fermentation is carried out in nutrient medium containing the antibiotic kanamycin. However, kanamycin is cleared in the manufacturing process and is not detectable in the final product. To produce pegfilgrastim-cbqv, a 20 kDa monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF.

Ziextenzo™ (pegfilgrastim-bmez)

Ziextenzo™ (pegfilgrastim-bmez) is a biosimilar to Neulasta® (pegfilgrastim). Pegfilgrastim-bmez is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a strain of E coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim-bmez, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF. The average molecular weight of pegfilgrastim-bmez is approximately 39 kD.

Biosimilars

As filgrastim and pegfilgrastim patents expire a variety of biosimilar products entered the market. Zarxio® was the first biosimilar filgrastim product, followed by Nivestym™. Fulphila™ is the first biosimilar pegfilgrastim product followed by Udenyca™ and then Ziextenzo™. Subsequent biosimilar products will be added to this policy as they appear.
Summary of Labeled Indications for G-CSF Products:

<table>
<thead>
<tr>
<th></th>
<th>Myelosuppressive Chemotherapy</th>
<th>Acute Myeloid Leukemia</th>
<th>Bone Marrow Transplant</th>
<th>Progenitor Cell Collection</th>
<th>Severe Chronic Neutropenia</th>
<th>Acute Radiation Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulphila™</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granix®</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neulasta®</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Neupogen®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nivestym™</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Udenyca™</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaxio®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ziextenzo™</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contraindications

Fulphila™, Granix®, Neulasta®, Neupogen®, Nivestym™, Udenyca™, Zaxio® and Ziextenzo™ are contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim products.

Benefit Application

Fulphila™, Granix®, Neulasta®, Neupogen®, Nivestym™, Udenyca™, Zaxio® and Ziextenzo™ may be managed under either the medical benefit (if administered by a provider) or pharmacy benefit (if administered by the patient or a nonprofessional caregiver).
Efficacy

Neupogen® (filgrastim) has been shown to be safe and effective in accelerating the recovery of neutrophil counts following a variety of chemotherapy regimens. In a phase III clinical trial in small cell lung cancer, the benefits of filgrastim over placebo were shown to be prevention of infection as manifested by febrile neutropenia, decreased hospitalization, and decreased IV antibiotic usage. No difference in survival or disease progression was demonstrated. Filgrastim is also indicated for use in adjunct to acute myeloid leukemia (AML) chemotherapy induction and consolidation. In a phase III clinical trial it was found to effectively reduce the duration of neutropenia, leading to significant clinical benefits by reducing the duration of fever; requirement for parenteral anti-infectives; and the duration of hospitalization. Filgrastim also has an indication for use in severe chronic neutropenia, in which a phase III clinical trial showed that the use of filgrastim resulted in a stimulation of bone marrow production and maturation of neutrophils, an increase in circulating neutrophils, and a reduction in the infection-related events. Filgrastim is also indicated for the use of stem cell harvest in donors.

Granix® (tbo-filgrastim) has been shown to be superior to placebo in duration of severe neutropenia (DSN) with a statistically significant reduction in DSN (1.1 days vs. 3.8 days, p < 0.0001). These results are from a phase III clinical trial in chemotherapy-naïve patients with high-risk stage II, stage III, or stage IV breast cancer.

Neulasta® (pegfilgrastim) has been shown safe and effective in accelerating the recovery of neutrophil counts. In a phase III study comparing pegfilgrastim to placebo, the incidence of hospitalizations (1% vs. 14%) and IV anti-infective use (2% vs. 10%) for the treatment of febrile neutropenia was lower in the pegfilgrastim treated patients compared to the placebo treated patients.

Comparative Effectiveness

In a Phase III study comparing pegfilgrastim to filgrastim as support for commonly used chemotherapy regimens, a single subcutaneous injection of pegfilgrastim provided adequate and safe neutrophil support comparable with daily subcutaneous injections of filgrastim in patients receiving commonly used standard-dose mild-to-moderate myelosuppressive chemotherapy regimens.

A Phase III clinical trial comparing pegfilgrastim to filgrastim for cytokine-alone mobilization of autologous hematopoietic stem and progenitor cells found that the total CD34+ cell yield was equivalent for both filgrastim- and pegfilgrastim-mobilized patients (80% vs. 91%, p = 0.44).
In a trial that compared fixed dose pegfilgrastim to daily filgrastim following autologous stem cell transplantations, it was found that there was no difference in outcomes in terms of safety and efficacy in a single dose of pegfilgrastim compared to 8 days of filgrastim.

In a single-blind, randomized, crossover trial comparing tbo-filgrastim to filgrastim, equivalence was demonstrated for the serum concentration profile, for the ANC profile, and for the CD34+ cell count, which is a marker for the ability of the GCSF to mobilize stem cells.

**Safety**

In clinical trials, the most common adverse events for filgrastim and peg-filgrastim was bone pain, which is often severe enough to require opioid analgesia. All three agents carry the risk of more serious adverse events, such as: splenic rupture, acute respiratory distress syndrome, serious allergic reactions, precipitation of severe sickle cell crisis in patients with sickle cell disorders, and the potential for tumor growth stimulatory effects on malignant cells.

**Choosing Wisely Guidelines**

ASCO guidelines recommend using white cell stimulating factors when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen, is greater than 20 percent and equally effective treatment programs that do not require white cell stimulating factors are unavailable (see Appendix).

Exceptions should be made when using regimens that have a lower chance of causing febrile neutropenia if it is determined that the patient is at high risk for this complication (due to age, medical history, or disease characteristics).

**2015 Update**

Added criteria and description for Zarxio® (filgrastim-sndz), a biosimilar to Neupogen that was recently approved by the FDA. A literature search from July 1, 2014, through October 31, 2015, did not identify any new evidence that would change the criteria for Neupogen, Neulasta, or Granix. This policy was reviewed by the Pharmacy and Therapeutics Committee November 19, 2015.
2016 Update

A literature search from July 1, 2015, through December 31, 2016, did not identify any new evidence that would change policy coverage.

2018 Update

A literature search from January 1, 2017, through January 30, 2018, did not identify any new evidence that would change policy coverage.

2019 Update

A literature search from January 1, 2018, through February 28, 2019, did not identify any new evidence that would change policy coverage. Updated references supporting interchangeability of biosimilars.

2020 Update

Reviewed prescribing information for all drugs listed in policy and conducted a literature search from January 1, 2019, through December 31, 2019. No new evidence was identified that would change coverage criteria. Added coverage criteria for Ziextenzo™ (pegfilgrastim-bmez) which is a biosimilar to Neulasta® (pegfilgrastim).

References


5. Granix Prescribing Information. North Wales, PA: Cephalon (Teva); 2013. Available at: November 12, 2015 27, 2014.


## Regimens with Predicted Risk of Febrile Neutropenia Greater Than 20%

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acronym</th>
<th>FN (%)</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin + Paclitaxel</td>
<td></td>
<td>21</td>
<td>Bladder</td>
</tr>
<tr>
<td>Methotrexate + Vinblastine + Doxorubicin + Cisplatin</td>
<td>MVAC</td>
<td>&gt; 20</td>
<td>Bladder</td>
</tr>
<tr>
<td>Docetaxel</td>
<td></td>
<td>21</td>
<td>Breast</td>
</tr>
<tr>
<td>Docetaxel + Trastuzumab</td>
<td></td>
<td>&gt; 20</td>
<td>Breast</td>
</tr>
<tr>
<td>Dose-dense Doxorubicin + Cyclophosphamide followed by Paclitaxel</td>
<td>DD AC followed by T</td>
<td>&gt; 20</td>
<td>Breast</td>
</tr>
<tr>
<td>Doxorubicin + Cyclophosphamide followed by Docetaxel</td>
<td>AC followed by Docetaxel</td>
<td>5-25</td>
<td>Breast</td>
</tr>
<tr>
<td>Docetaxel followed by Doxorubicin + Cyclophosphamide</td>
<td>Docetaxel followed by AC</td>
<td>40</td>
<td>Breast</td>
</tr>
<tr>
<td>Doxorubicin + Docetaxel</td>
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<td>33-48</td>
<td>Breast</td>
</tr>
<tr>
<td>Doxorubicin + Paclitaxel</td>
<td></td>
<td>21-32</td>
<td>Breast</td>
</tr>
<tr>
<td>Docetaxel + Doxorubicin + Cyclophosphamide</td>
<td>TAC</td>
<td>22-25</td>
<td>Breast</td>
</tr>
<tr>
<td>Dose-dense Cyclophosphamide + Epirubicin + Fluorouracil</td>
<td>DD FEC</td>
<td>71</td>
<td>Breast</td>
</tr>
<tr>
<td>Dose-dense Doxorubicin followed by Paclitaxel followed by Cyclophosphamide</td>
<td></td>
<td>&gt; 20</td>
<td>Breast</td>
</tr>
<tr>
<td>Dose-dense Epirubicin + Cyclophosphamide</td>
<td></td>
<td>&gt; 20</td>
<td>Breast</td>
</tr>
<tr>
<td>Cyclophosphamide + Epirubicin + Fluorouracil + Docetaxel</td>
<td>FEC-D</td>
<td>25-46</td>
<td>Breast</td>
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<td>Fractionated cyclophosphamide + Vincristine + Doxorubicin + Dexamethasone + Rituximab</td>
<td>Hyper CVAD + Rituximab</td>
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<td>Burkitt’s Lymphoma</td>
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<td>Paclitaxel + Cisplatin</td>
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<td>Esophageal/Gastric</td>
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<td>Bleomycin + Vincristine + Cisplatin followed by Cisplatin + Ifosfamide + Etoposide</td>
<td>BOP followed by VIP</td>
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<td>Germ Cell</td>
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<td>Vinblastine + Ifosfamide + Cisplatin</td>
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<td>67-71</td>
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<td>FN (%)</td>
<td>Cancer</td>
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<td>Hodgkin's</td>
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<td>Doxorubicin + Bleomycin + Vinblastine + Dacarbazine</td>
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<td>Dacarbazine + Cisplatin + Vinblastine</td>
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<td>LVFU-irinotecan</td>
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<td>Docetaxel + Cyclophosphamide</td>
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<td>Decitabine</td>
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<td>Acronym</td>
<td>FN (%)</td>
<td>Cancer</td>
</tr>
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<td>DD ACBVP</td>
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<td>NHL/CLL</td>
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<td>Fludarabine + Cyclophosphamide + Rituximab</td>
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<td>Ovarian</td>
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<td>Acronym</td>
<td>FN (%)</td>
<td>Cancer</td>
</tr>
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<tr>
<td>Dose-dense Ifosfamide + Carboplatin + Etoposide</td>
<td>DD ICE</td>
<td>&gt; 20</td>
<td>SCLC</td>
</tr>
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<td>Dose-dense Cyclophosphamide + Doxorubicin + Vincristine followed by Cisplatin + Etoposide</td>
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<td>SCLC</td>
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<td>Mesna + Doxorubicin + Ifosfamide + Dacarbazine</td>
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<td>Doxorubicin</td>
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<td>Soft Tissue Sarcoma</td>
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<tr>
<td>Ifosfamide + Doxorubicin</td>
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<td>&gt; 20</td>
<td>Soft Tissue Sarcoma</td>
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<td>Vinblastine + Ifosfamide + Cisplatin</td>
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<td>&gt; 20</td>
<td>Testicular</td>
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<td>Etoposide + Ifosfamide + Cisplatin</td>
<td>VIP</td>
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<td>Testicular</td>
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<tr>
<td>Bleomycin + Etoposide + Cisplatin</td>
<td>BEP</td>
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<td>Testicular</td>
</tr>
<tr>
<td>Paclitaxel + Ifosfamide + Cisplatin</td>
<td>TIP</td>
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<td>Testicular</td>
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<tr>
<td>Paclitaxel + Carboplatin</td>
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<td>Urothelial</td>
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<tr>
<td>Methotrexate + Vinblastine + Doxorubicin + Cisplatin</td>
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<td>26</td>
<td>Urothelial</td>
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<tr>
<td>Dose-dense Methotrexate + Vinblastine + Doxorubicin + Cisplatin</td>
<td>DD MVAC</td>
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<td>Urothelial</td>
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Source: Smith, 2006

### History

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<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>03/10/14</td>
<td>New policy. This policy is added to the Prescription Drug section and covers three granulocyte colony-stimulating factors: tbo-filgrastim (Granix®), filgrastim (Neupogen®) and pegfilgrastim (Neulasta®). All are considered medically necessary when criteria are met for conditions and per treatment guidelines outline in this policy. Policy approved with a hold for provider notification; it will be effective August 30, 2014.</td>
</tr>
<tr>
<td>08/11/14</td>
<td>Coding update. HCPCS codes J1442, J1446 and J2505 added to the policy.</td>
</tr>
<tr>
<td>10/13/14</td>
<td>Interim update. Policy reformatted to clarify details of step therapy in the use of GCSF; criteria added for making exceptions due to geographical issues.</td>
</tr>
<tr>
<td>02/10/15</td>
<td>Coding update. HCPCS code J1446 removed from policy; this is not being reviewed at this time.</td>
</tr>
<tr>
<td>12/08/15</td>
<td>Annual Review. Policy updated with literature review. Filgrastim-sndz (Zarxio) added to the medical necessity policy statements. Reviewed and approved by P&amp;T Committee</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
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<tr>
<td>November 2015</td>
<td>Added HCPCS code Q5101.</td>
</tr>
<tr>
<td>02/09/16</td>
<td>Interim Review. Policy scope clarified to apply only to adults, age 18 and over.</td>
</tr>
<tr>
<td>10/01/16</td>
<td>Policy moved into new format; no change to policy statements.</td>
</tr>
<tr>
<td>04/01/17</td>
<td>Annual Review, approved March 14, 2017. No changes to criteria made. Added a new reference to the bibliography section (#15).</td>
</tr>
<tr>
<td>03/01/18</td>
<td>Annual Review, approved February 27, 2018. Minor change made to criteria. Deletion of first cycle of chemotherapy within the criteria. HCPCS code J1447 added to policy.</td>
</tr>
<tr>
<td>03/09/18</td>
<td>Coding update, added CPT code 96377.</td>
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<tr>
<td>04/01/18</td>
<td>Interim Review, approved March 20, 2018. Added “Neulasta Onpro®” for clarity.</td>
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<tr>
<td>01/01/19</td>
<td>Interim Review, approved December 19, 2018. Added Udenyca (pegfilgrastim-cbqv) criteria. Added use of Nivestym (filgrastim-aafi) as qualifier to second-line therapy. Added new HCPS code Q5110 (new code effective 1/1/19).</td>
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<tr>
<td>06/01/19</td>
<td>Coding update, added HCPCS code Q5111 (new code effective 1/1/19).</td>
</tr>
<tr>
<td>09/01/19</td>
<td>Interim Review, approved August 13, 2019. Added for targeted uses patients undergoing autologous peripheral blood progenitor cell collection and patients acutely exposed to myelosuppressive doses of radiation. Removed reference to Geographic Challenge and expanded to a valid medical rationale for why self-injection or home nursing cannot be performed.</td>
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<tr>
<td>02/01/20</td>
<td>Annual Review, approved January 9, 2020. Added coverage criteria for Ziestenzo (pegfilgrastim-bmez) which is a biosimilar to Neulasta (pegfilgrastim). Added HCPCS code J3590 to report Ziestenzo.</td>
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</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

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Toll free 855-332-4535, Fax 425-918-5952. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan laadann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konse nan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kék aksyon avan seten dat limit pou ka renbe kouvèti asirans sante w lan oswa pou yo ka ede w avèk depans yo. Se dwa w pou reseva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peyeye sou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

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Illokoo (Ilocano):
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800-722-1471 (TTY: 800-842-5357)