AETNA BETTER HEALTH®

Non-Formulary Prior Authorization guideline for Colony Stimulating Factor (CSF)/ Myeloid Growth Factor (MGF)

Applicable Agents:
- Fulphila™ (pegfligrastim-jmdb)
- Granix® (tbo-filgrastim)
- Leukine ® (sargramostim; GM-CSF)
- Neulasta Onpro® (peg-filgrastim; G-CSF)
- Neulasta® (peg-filgrastim; G-CSF)
- Neupogen ® (filgrastim; G-CSF)
- Nivestym™ (filgrastim-aafi)
- Udenyca™ (pegfilgrastim-cbqv)
- Zarxio® (filgrastrim-sndz)

Preferred Agents:
- **Zarxio and Nivestym are the preferred short acting Granulocyte Colony Stimulating Factors (G-CSF). Requests for non-preferred short acting agents require trial of Zarxio and Nivestym in addition to meeting the clinical criteria detailed below.**
- **Fulphila and Udenyca are the preferred long acting Granulocyte Colony Stimulating Factors (G-CSF). Requests for non-preferred long acting agents require trial of Fulphila and Udenyca in addition to meeting the clinical criteria detailed below.**

General Authorization Criteria for ALL Agents and Indications:
A. Prescribed by, or in consultation with, a hematologist or oncologist
B. Medical records, including labs and weight or body surface area (BSA), to support diagnosis and dosing is submitted with request
C. Requested agent is dosed and administered within FDA labeled recommendations
   1. Will not be used concomitantly with radiation AND chemotherapy
   2. Will be administered at the appropriate time after chemotherapy OR radiation
D. Patient does not have any contraindications to the requested agent
E. Will not be used in combination with other myeloid growth factors
**Additional Criteria Based on Indication:**

A. Chemotherapy-Induced Febrile Neutropenia: (Fulphila, Granix, Leukine, Neulasta, Neupogen, Nivestym, Udenyca and Zarxio)

1. Member is receiving chemotherapy for a NON-myeloid cancer (for example, solid tumor, lymphoma)
   a. For PRIMARY prophylaxis:
      i. Member meets ONE of the following:
         a. Chemotherapy regimen is given after bone marrow transplant; OR
         b. Chemotherapy regimen has >20% risk of febrile neutropenia; OR
         c. Chemotherapy regimen has 10%-20% risk of febrile neutropenia AND Member has ANY of the following risk factors for febrile neutropenia:
            i. age > 65 years
            ii. prior chemotherapy or radiation therapy
            iii. persistent neutropenia
            iv. bone marrow involvement by tumor
            v. Recent surgery and or open wounds
            vi. Liver dysfunction (bilirubin > 2.0)
            vii. Renal dysfunction (CRCL <50)
            viii. HIV
            ix. Additional risk factor(s) supported by compendia (e.g. NCCN, ESMO, ASCO)
   b. For SECONDARY prophylaxis (Fulphila, Granix, Leukine, Neulasta, Neupogen, Nivestym, Udenyca and Zarxio): Member previously experienced febrile neutropenia from the same chemotherapy regimen and reducing or delaying chemotherapy dose may compromise treatment outcome
c. For TREATMENT of febrile neutropenia (Leukine, Neupogen, Nivestym, and Zarxio) in members who did NOT receive CSF prophylaxis: Member 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)

d. For TREATMENT of febrile neutropenia (Leukine, Neupogen, Nivestym, and Zarxio) in members who are receiving daily prophylactic CSF prophylaxis. Use in members on long-lasting prophylactic pegfilgrastim is not recommended.

B. Severe chronic congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia: (Nivestym, Neupogen and Zarxio)
   1. Member has ONE of the following:
      i. Evidence of inadequate bone marrow reserve (e.g., recurrent fevers, splenomegaly, mucosal ulcers, abdominal pain)
      ii. High risk for developing serious bacterial infection (e.g., primarily severe neutropenia, indwelling venous catheters, prior serious infections)
      iii. Current bacterial infection

C. Neutropenia related to Human Immunodeficiency Virus (HIV) or drug therapy; ganciclovir or zidovudine induced: (Leukine Neupogen, Nivestym, and Zarxio):
   1. Prescribed by, or in consultation with an Infectious Disease Specialist, Hematologist, or Human Immunodeficiency Virus (HIV) Specialist

D. Neupogen, Nivestym and Zarxio may also be reviewed for medical necessity for treatment of the following indications:
   1. Acute Myeloid Leukemia in Members receiving induction or consolidation chemotherapy
   2. Mobilization of hematopoietic progenitor cells before autologous stem cell transplant
   3. Mobilization of hematopoietic progenitor cells in the donor before allogenic stem cell transplant

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Current PARP Approval: 2/2019
4. Treatment of acute radiation exposure, to increase survival, in Members who receive myelosuppressive doses of radiation at a dose of 2 gray (Gy)
5. Myelodysplastic Syndrome (MDS) or aplastic anemia

E. Leukine may also be reviewed for medical necessity for treatment of the following indications:
   1. Acute Myeloid Leukemia after induction chemotherapy for members age 55 years or older
   2. Bone marrow transplant failure or engraftment delay
   3. Myeloid reconstitution after allogenic bone marrow transplant
   4. Myeloid reconstitution after autologous bone marrow transplant in Members with Hodgkin's disease, non-Hodgkin's lymphoma, or acute lymphocytic leukemia
   5. Before and after autologous peripheral blood stem cell transplantation
   6. Patients acutely exposed to myelosuppressive doses of radiation, administer once daily as subcutaneous injection.

Authorization and Limitations

Initial Approval
1. Chemotherapy-induced neutropenia (primary or secondary prophylaxis):
   a. Approve per cycle of chemotherapy:
      i. up to a 14 day supply for Neupogen, Nivestym and Zarxio or
      ii. one (1) 6mg dose of Neulasta, FulPhila, Udenyca no less than every 14 days
      iii. include refills if number of cycles is provided
2. Treatment of Neutropenia (e.g., congenital, cyclic, or idiopathic, or after chemo + BMT):
   a. Approve for 3 months
3. For other indications
   a. Up to six months or less

Renewal:
1. Chemotherapy-induced neutropenia (primary or secondary prophylaxis):
   a. Recent absolute neutrophil count (ANC) showing a response to therapy
b. Approve per cycle of chemotherapy:
   i. up to a 14 day supply for Neupogen, Nivestym and Zarxio
   ii. one (1) 6mg dose of Neulasta Fulphila, Udenyca no less than every 14 days
   iii. Include refills if number of cycles is provided
2. All other indications:
   a. Recent absolute neutrophil count (ANC), complete blood count (CBC), and/or platelet counts
   b. Approve up to one year

Additional Information:

**Note:** Neutropenia is defined as an absolute neutrophil count (ANC) of < 500 neutrophils/mcL or an absolute neutrophil count (ANC) of < 1000 neutrophils/mcL and a predicted decline to < than or equal to 500 neutrophils/mcL over the next 48 hours.

**Determining the risk of febrile neutropenia:**
A member’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 member’s chemotherapy regimen in addition to the presence of other member-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%.

**Dosing Table:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Available Dosage forms</th>
</tr>
</thead>
</table>
| Neupogen Nivestym Zarxio | Febrile Neutropenia (FN) or acute myeloid leukemia (AML): 5 mcg/kg/day (Not given 24 hours before chemotherapy and 24 hours after)  
Bone marrow transplant (BMT): 10 mcg/kg/day (given 24 hrs. after bone marrow transplant (BMT) and given for at least 24 hours)  
Peripheral Blood Progenitor Cell (PBPC): 10 mcg/kg/day; at least 4 days before and up to 7 days  
Severe Chronic Neutropenia:  
- Idiopathic neutropenia: 1.2 mcg/kg/day  
- Cyclic neutropenia: 2.1 mcg/kg/day  
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day  
Radiation exposure: 10mg/kg (give immediately after exposure and GY > 2) | Vials:  
- 300 mcg/mL, single-dose vial  
- 480 mcg/1.6 mL, single-dose vial  
Prefilled Syringe:  
- 300 mcg/0.5 mL per syringe  
- 480 mcg/0.8 mL per syringe |
| Fulphila Neulasta Udenyca | Febrile Neutropenia-5mcg/kg/day  
Not given 24 hours before chemotherapy and 24 hours after chemotherapy. | 6 mg/0.6 mL, single-dose prefilled syringe  
6 mg/0.6 mL, single-dose prefilled syringe co-packaged with |
| Leukine | • Acute myeloid leukemia (AML): 250 mcg/m²/day subcutaneous (SQ) or intravenous (IV) on day 11 or 4 days following the completion of induction chemotherapy  
• Mobilization of peripheral blood progenitor cells: 250 mcg/m²/day administered intravenously over 24 hours or subcutaneous injection once daily.  
• Myeloid reconstitution after autologous or allogeneic BMT (bone marrow transplant): 250 mcg/m²/day administered intravenously over a 2-hour period  
• BMT failure or engraftment delayed: 250 mcg/m²/day for 14 days as a 2-hour intravenous infusion.  
• Patients acutely exposed | • 500 mcg/mL vial  
• 250 mcg powder for injection |
Granix

- Febrile Neutropenia (FN)
  5mcg/kg/day
  subcutaneous (SQ) injection
- Not given 24 hours before chemotherapy and 24 hours after chemotherapy

- 300 mcg/0.5 mL, single-use prefilled syringe
- 480 mcg/0.8 mL, single-use prefilled syringe

Colony Stimulating Factors are NOT covered for members with the following criteria:
- Use not approved by the FDA; AND
- The use is unapproved and not supported by the literature or evidence as an accepted off-label use.

**Medically Necessary** — A service or benefit is Medically Necessary if it is compensable under the MA Program and if it meets any one of the following standards:

- The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.

- The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.

- The service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age.

Determination of Medical Necessity for covered care and services, whether made on a Prior Authorization, Concurrent Review, Retrospective Review, or exception basis, must be documented in writing.

The determination is based on medical information provided by the Member, the Member’s family/caretaker and the Primary Care Practitioner, as well as any other Providers, programs, agencies that have evaluated the Member.

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All such determinations must be made by qualified and trained Health Care Providers. A Health Care Provider who makes such determinations of Medical Necessity is not considered to be providing a health care service under this Agreement.

References:

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Myeloid Growth
13. Fulphila (pegfilgrastim-jmdb) [prescribing information]. Rockford, IL: Mylan Institutional LLC; June 2018

### Table: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of 20% or Higher

<table>
<thead>
<tr>
<th>Cancer Histology</th>
<th>Treatment Setting</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Lymphoblastic Leukemia (ALL)</td>
<td>Induction</td>
<td>ALL induction regimens (see NCCN guidelines)</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>Neoadjuvant, adjuvant, metastatic</td>
<td>MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)</td>
</tr>
<tr>
<td></td>
<td>Prior adjuvant allowed</td>
<td>CBDCa/Pac (carboplatin, paclitaxel)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>Metastatic or relapsed</td>
<td>Docetaxel + trastuzumab</td>
</tr>
<tr>
<td></td>
<td>Adjuvant</td>
<td>Dose-dense AC followed by T (doxorubicin, cyclophosphamide, paclitaxel)</td>
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<tr>
<td></td>
<td>Adjuvant</td>
<td>TAC (docetaxel, doxorubicin, cyclophosphamide)</td>
</tr>
<tr>
<td></td>
<td>Metastatic (1st line)</td>
<td>AT (doxorubicin, docetaxel)</td>
</tr>
<tr>
<td></td>
<td>Metastatic (2nd line)</td>
<td>Doc (docetaxel)</td>
</tr>
<tr>
<td>Esophageal and Gastric Cancers</td>
<td></td>
<td>Docetaxel/cisplatin/fluorouracil</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td></td>
<td>BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)</td>
</tr>
<tr>
<td>Kidney Cancer</td>
<td></td>
<td>Doxorubicin/gemcitabine</td>
</tr>
</tbody>
</table>

Last Review: 1/2019
Previous PARP Approval: 1/2019
Current PARP Approval: 2/2019
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<thead>
<tr>
<th>Non-Hodgkin's Lymphoma</th>
<th>Diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphomas (PTCL), 2nd line</th>
<th>ICE (ifosfamide, carboplatin, etoposide)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RICE (rituximab, ifosfamide, carboplatin, etoposide)</td>
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<tr>
<td></td>
<td></td>
<td>CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab</td>
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<tr>
<td></td>
<td>DLBCL, 2nd line, refractory</td>
<td>MINE (mesna, ifosfamide, novantrone, etoposide)</td>
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<tr>
<td></td>
<td>PTCL, DLBCL, 2nd line</td>
<td>DHAP (dexamethasone, cisplatin, cytarabine)</td>
</tr>
<tr>
<td></td>
<td>DLBCL, PTCL, 2nd line, recurrent</td>
<td>ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine (Ara-C))</td>
</tr>
<tr>
<td></td>
<td>Relapsed</td>
<td>HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Advanced, metastatic, or recurrent</td>
<td>Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine)</td>
</tr>
<tr>
<td></td>
<td>Advanced, metastatic, or recurrent</td>
<td>Dacarbazine-based combination with IL-2, interferon alpha (dacarbazine, cisplatin, vinblastine, IL-2, interferon alpha)</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td></td>
<td>Topotecan</td>
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<td></td>
<td></td>
<td>Paclitaxel</td>
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<td></td>
<td></td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>Advanced or metastatic</td>
<td>FOLFIRINOX (leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin)</td>
</tr>
<tr>
<td>Soft Tissue Sarcoma</td>
<td></td>
<td>MAID (mesna, doxorubicin, ifosfamide, dacarbazine)</td>
</tr>
<tr>
<td>Cancer Histology</td>
<td>Treatment Setting</td>
<td>Regimen</td>
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<td>----------------------------------</td>
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<tr>
<td>Occult primary - adenocarcinoma</td>
<td></td>
<td>Gemcitabine/docetaxel</td>
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<tr>
<td>Breast cancer</td>
<td></td>
<td>Docetaxel every 21 days</td>
</tr>
<tr>
<td>Adjuvant</td>
<td></td>
<td>CMF classic (cyclophosphamide, methotrexate, fluorouracil)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td></td>
<td>CA (doxorubicin, cyclophosphamide) (60 mg/m2) (hospitalized)</td>
</tr>
<tr>
<td>Adjuvant (taxane portion only)</td>
<td></td>
<td>AC (doxorubicin, cyclophosphamide) + sequential docetaxel</td>
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<tr>
<td>Adjuvant</td>
<td></td>
<td>AC + sequential docetaxel + trastuzumab</td>
</tr>
<tr>
<td>Metastatic (1st line)</td>
<td></td>
<td>A (doxorubicin) (75)</td>
</tr>
<tr>
<td>Metastatic (1st line)</td>
<td></td>
<td>AC (doxorubicin, cyclophosphamide)</td>
</tr>
<tr>
<td>Metastatic (2nd line)</td>
<td></td>
<td>CapDoc (capecitabine, docetaxel)</td>
</tr>
<tr>
<td>Metastatic or relapsed</td>
<td></td>
<td>FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel</td>
</tr>
</tbody>
</table>

Source: Smith, et al., 2006; NCCN, 2016.

Table: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of 10% to 19%
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Cancer</td>
<td>TC (docetaxel, cyclophosphamide)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>FOLFOX (fluorouracil, leucovorin, oxaliplatin)</td>
</tr>
<tr>
<td>Advanced</td>
<td>FL (fluorouracil, leucovorin)</td>
</tr>
<tr>
<td>Advanced (one prior chemo allowed)</td>
<td>CPT-11 (irinotecan) (350 mg/m2 q 3 wk)</td>
</tr>
<tr>
<td>Esophageal and Gastric Cancers</td>
<td>Irinotecan/cisplatin</td>
</tr>
<tr>
<td></td>
<td>Epirubicin/cisplatin/5-fluorouracil</td>
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<tr>
<td></td>
<td>Epirubicin/cisplatin/capecitabine</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Induction Cis/Doc/5-FU (cisplatin, docetaxel, 5-fluorouracil)</td>
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<tr>
<td>Multiple myeloma</td>
<td>DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)</td>
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<tr>
<td></td>
<td>DT-PACE + bortezomib (VTD-PACE)</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphomas</td>
<td>AIDS-related NHL, Burkitt lymphoma, recurrent, other NHL subtypes</td>
</tr>
<tr>
<td></td>
<td>EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)</td>
</tr>
<tr>
<td></td>
<td>AIDS-related NHL, DLBCL, recurrent</td>
</tr>
<tr>
<td></td>
<td>EPOCH-IT chemotherapy</td>
</tr>
<tr>
<td></td>
<td>DLBCL, PTCL, 2nd line</td>
</tr>
<tr>
<td></td>
<td>GDP (gemcitabine, dexamethasone, cisplatin)</td>
</tr>
<tr>
<td></td>
<td>DLBCL, 2nd line, Burkitt lymphoma, other NHL subtypes</td>
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<tr>
<td></td>
<td>GDP (gemcitabine, dexamethasone, cisplatin) + rituximab</td>
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<td></td>
<td>FMR (fludarabine, mitoxantrone, rituximab)</td>
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<tr>
<td></td>
<td>CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) including regimens with pegylated liposomal doxorubicin or mitoxantrone substituted for doxorubicin</td>
</tr>
<tr>
<td>Non-Small Cell Lung Cancer</td>
<td>Advanced/metastatic</td>
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<tr>
<td></td>
<td>Cisplatin/paclitaxel</td>
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<td></td>
<td>Adjuvant, advanced/metastatic</td>
</tr>
<tr>
<td></td>
<td>Cisplatin/vinorelbine</td>
</tr>
<tr>
<td>Cancer Type</td>
<td>Treatment Options</td>
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<td>----------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Adjuvant, advanced/metastatic</td>
<td>Cisplatin/docetaxel</td>
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<tr>
<td>Adjuvant, advanced/metastatic</td>
<td>Cisplatin/etoposide</td>
</tr>
<tr>
<td>Adjuvant, advanced/metastatic</td>
<td>Carboplatin/paclitaxel</td>
</tr>
<tr>
<td>Advanced/metastatic</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>Carboplatin/docetaxel</td>
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<tr>
<td>Pancreatic Cancer</td>
<td>FOLFIRINOX</td>
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<td>Prostate Cancer</td>
<td>Cabazitaxel</td>
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<td>Small Cell Lung Cancer</td>
<td>Etoposide/carboplatin</td>
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<tr>
<td>Testicular Cancer</td>
<td>Etoposide/carboplatin</td>
</tr>
<tr>
<td>Uterine Sarcoma</td>
<td>Advanced or metastatic</td>
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</tbody>
</table>

Docetaxel