COVERAGE POLICY

This Coverage Policy applies to Individual Health Insurance Marketplace benefit plans only.

Colony Stimulating Factor Therapy Policy

SUBJECT
Colony Stimulating Factor (CSF) Therapy:

a. Granulocyte-macrophage colony stimulating factor (GM-CSF) – Leukine™ (sargramostim); and
b. Granulocyte colony stimulating factors (G-CSF) – Neupogen™ (filgrastim) and Neulasta™ (pegfilgrastim)

PURPOSE
To define the criteria to be used to determine the medical necessity of Colony Stimulating Factor Therapy.

COVERAGE POLICY

1) Granulocyte colony-stimulating factor (G-CSF; filgrastim [Neupogen], pegfilgrastim [Neulasta], or
granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim [Leukine, Prokine]) for the
prevention of febrile neutropenia (FN) is medically necessary in adult and pediatric members with cancer
for any of the following indications:
   a) Primary prophylaxis
      a. Individuals with non-myeloid malignancies receiving myelosuppressive chemotherapy that is
         expected to result in a 20% or higher incidence of FN (see appendix); or
         Note: In the absence of special circumstances, most commonly used regimens have risks of FN
         of less than 20%. When available, alternative regimens offering equivalent efficacy, but not
         requiring CSF support, should be utilized (Smith et al, 2006).
      b. Individuals receiving non-myelosuppressive chemotherapy who are considered to be at high risk for
         chemotherapy-induced FN infectious complications because of bone marrow compromise or co-
         morbidities, including any of the following (not an all-inclusive list):
            a. Active infections or open wounds;
            b. Age greater than 65 years;
            c. Bone marrow involvement by tumor producing cytopenias;
            d. Extensive prior treatment including large radiation ports;
            e. Poor nutritional status;
            f. Poor performance status
            g. Previous episodes of FN;
            h. Other serious co-morbidities.
   b) Secondary prophylaxis for members who experienced a febrile neutropenic complication from a prior
      cycle of chemotherapy (for which primary prophylaxis was not received).
      Note: Colony-stimulating factors should not be routinely used for afebrile neutropenia (Smith et al,
      2006).
   c) Therapeutic use in high-risk, febrile, neutropenic members who have any of the following prognostic
      factors that are predictive of clinical deterioration:
         i) Age greater than 65 years;
         ii) Being hospitalized at the time of the development of fever;
         iii) Hypotension;
         iv) Invasive fungal infection;
         v) Multi-organ dysfunction;
         vi) Pneumonia;
vii) Prolonged (greater than 10 days) and profound (absolute neutrophil count less than 1 x 10⁹/L) neutropenia;

viii) Uncontrolled primary disease.

d) To increase dose intensity chemotherapy regimens in settings where clinical research demonstrates that dose-intensive therapy produces improvement in disease control, when these therapies are expected to produce significant rates of FN (i.e., 20 % or higher incidence of FN).

e) Individuals with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy.

f) Individuals with acute lymphoblastic leukemia (ALL) after completion of the first few days of chemotherapy of the initial induction or first post-remission course.

g) Individuals receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.

h) Individuals with lymphoma aged 65 years and older treated with curative chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] or more aggressive regimens).

i) Reduction in the duration of neutropenia and neutropenia-related infectious complications in members with non-myeloid malignancies undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplantation (BMT).

j) As adjunct to progenitor cell-transplantation to mobilize peripheral-blood progenitor-cells (PBPC) often in conjunction with chemotherapy and their administration after autologous, but not allogeneic transplant.  
   Note: Neulasta (pegfilgrastim) is not currently indicated for stem cell mobilization.

k) Intermittent use in members with myelodysplastic syndromes who have less than 15 % blasts in their bone marrow or are experiencing recurrent neutropenic infections.

l) As treatment for radiation injury at doses of 3 to 10 Grays (Gy) or above.

2) Aetna considers granulocyte colony-stimulating factor (G-CSF; filgrastim [Neupogen], pegfilgrastim [Neulasta]; or granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim [Leukine, Prokine]) medically necessary for the prevention of febrile neutropenia in adult and pediatric members with either of the following non-oncologic indications:

a) Chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia; or

b) Individuals with advanced HIV infection and neutropenia (absolute neutrophil count less than 1 x 10⁹/L) to allow scheduled dosing of myelosuppressive anti-retroviral medication (e.g., zidovudine and ganciclovir).

AUTHORIZATION PERIOD AND LIMITATIONS

Initial approval:  6 months

Extended approval:  Additional 6 months or longer authorization period per Medical Director’s clinical judgment.

PROCUREMENT:

Neupogen  J-code: J1440, J1441

Neulasta  J-code: J2505

Leukine  J-code: J2820

Specialty pharmacy source: Aetna Specialty Pharmacy (ASRx)

Contact:

ASRx toll free number:  (866) 782-2779

ASRx toll free fax number:  (866) 329-2779

ASRx e-mail address:  www.AetnaSpecialtyPharmacy.com
REFERENCES

83. del Giglio A, Eniu A, Ganea-Motan D, et al. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer. 2008;8:332.
91. All Wales Medicines Strategy Group (AWMSG). Filgrastim (TevaGrastim®):AWMSG Secretariat Assessment Report Advice No. 1410. Penarth, UK: All Wales Therapeutics and Toxicology Centre (AWTTC), secretariat of the All Wales Medicines Strategy Group (AWMSG); 2010.


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Appendix A

Table A: Febrile Neutropenia with Selected Chemotherapy Regimens (CSF use indicated for primary prophylaxis with myelosuppressive chemotherapy which presents risk of febrile neutropenia ≥20%).

This list is not comprehensive; there are other agents/regimens that have a high risk for the development of febrile neutropenia.

<table>
<thead>
<tr>
<th>Cancer Histology</th>
<th>Stage &amp; Prior Therapy</th>
<th>Regimen</th>
<th>Febrile Neutropenia (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Neoadjuvant/Adjuvant/Metastatic</td>
<td>MVAC²</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Bladder</td>
<td>Prior adjuvant allowed</td>
<td>CBDCA/Pac</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Breast</td>
<td>Metastatic or Relapsed</td>
<td>DocT</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Breast</td>
<td>Adjuvant</td>
<td>TAC</td>
<td>23.8</td>
<td>3</td>
</tr>
<tr>
<td>Breast</td>
<td>Metastatic 1st line</td>
<td>AT</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Breast</td>
<td>Metastatic 1st line</td>
<td>TAC</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Breast</td>
<td>Metastatic 2nd line</td>
<td>Doc</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Cervix</td>
<td>1st line</td>
<td>TC</td>
<td>27.7</td>
<td>1</td>
</tr>
<tr>
<td>Gastric</td>
<td>Advanced</td>
<td>DCF</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Germ cell</td>
<td>Relapsed</td>
<td>VeIP</td>
<td>71</td>
<td>3</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>VIP</td>
<td>&gt;20%³</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Germ Cell</td>
<td>Metastatic 1st line</td>
<td>BEP</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>Relapse 2nd line</td>
<td>TIP</td>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td>Head/Neck</td>
<td>Recurrent Metastatic</td>
<td>TIMCDDP</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>Advanced</td>
<td>BEACOPP</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>Kidney</td>
<td>Metastatic</td>
<td>GemDoc</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>Lung, SCLC</td>
<td>Recurrent</td>
<td>Top</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Lung, SCLC</td>
<td>Newly diagnosed</td>
<td>CAE</td>
<td>57% (1st cycle); 77% (all cycles)</td>
<td>1</td>
</tr>
<tr>
<td>Lung, SCLC</td>
<td>Extensive/Untreated</td>
<td>TopT</td>
<td>&gt;20%³</td>
<td>1</td>
</tr>
<tr>
<td>Lung, SCLC</td>
<td>Advanced/Metastatic</td>
<td>CBDCA/Doc</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Lung, SCLC</td>
<td>Advanced/Metastatic</td>
<td>VIG</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>NHL</td>
<td>Intermediate-high grade, untreated</td>
<td>CHOP(+G-CSF)</td>
<td>80-82</td>
<td>1</td>
</tr>
<tr>
<td>NHL</td>
<td>Relapsed/Refractory</td>
<td>CFAR</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>NHL</td>
<td>Relapsed/Refractory</td>
<td>ICE</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>NHL</td>
<td>Relapsed/Refractory</td>
<td>RICE</td>
<td>21.6</td>
<td>2</td>
</tr>
<tr>
<td>NHL</td>
<td>Relapsed/Refractory</td>
<td>CHOP-14±R</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>NHL</td>
<td>Relapsed/Refractory</td>
<td>MINE</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>NHL</td>
<td>1st line, Relapse/Refractory</td>
<td>HyperCVAD+R</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>NHL</td>
<td>Relapsed</td>
<td>VAPEC-B</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>NHL</td>
<td>Relapsed</td>
<td>ESHAP</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>NHL</td>
<td>Relapsed</td>
<td>DHAP</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>NHL</td>
<td></td>
<td>A(N)CVB</td>
<td>78</td>
<td>1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Advanced/Metastatic/Recurrent</td>
<td>DCV</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Advanced/Metastatic/Recurrent</td>
<td>DCV+IL2/IFNa</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome</td>
<td>1st line</td>
<td>Tgb/CsA</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome</td>
<td>Prior therapy allowed</td>
<td>Dec</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Ovary</td>
<td>Salvage</td>
<td>Top</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Ovary</td>
<td>Refractory</td>
<td>Pac</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Ovary</td>
<td>Refractory to paclitaxel</td>
<td>Doc</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Soft Tissue Sarcoma</td>
<td>Inoperable metastatic</td>
<td>MAID</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>Soft Tissue Sarcoma</td>
<td>Advanced</td>
<td>A</td>
<td>&gt;20%³</td>
<td>2</td>
</tr>
<tr>
<td>Soft Tissue Sarcoma</td>
<td>Primary/Metastatic</td>
<td>IA</td>
<td>48.5</td>
<td>2</td>
</tr>
</tbody>
</table>

¹Source key:
1= Colony Stimulating Factor Policy-Coventry Health Care, Inc. (Last update 4/13)

2MVAC =methotrexate, vinblastine, doxorubicin, cisplatin; CBDCA/Pac=carboplatin, paclitaxel; DocT= docetaxel, trastuzumab; TAC=docetaxel, doxorubicin, cyclophosphamide; A=doxorubicin; T=docetaxel; C=cyclophosphamide; Doc=docetaxel; DCF=docetaxel, cisplatin, fluorouracil; VeiP=vinblastine, ifosfamide, cisplatin; VIP=etoposide, ifosfamide, cisplatin; BEP=bleomycin, etoposide, cisplatin; TIP=paclitaxel, ifosfamide, cisplatin; TIMCDDP=paclitaxel, ifosfamide, mesna, cisplatin; BEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GemDoc=gemcitabine, docetaxel; Top=topotecan; CAE=cyclophosphamide, docetaxel, etoposide; TopT=topotecan, paclitaxel; CBDCA/Doc=carboplatin, docetaxel; VIG=vinorelbine, ifosfamide, gemcitabine; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab; CFAR=cyclophosphamide, fludarabine, alemtuzumab, rituximab; ICE=ifosfamide, cisplatin, etoposide; RICE=rituximab, ifosfamide, cisplatin, etoposide; CHOP-14=cyclophosphamide, doxorubicin, vincristine, prednisone; R=rituximab; MINE=mesna, ifosfamide, vinorelbine, etoposide; HyperCVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone; VAPEC-B=vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin; ESHAP=etoposide, methylprednisone, cisplatin, cytarabine; DHAP=dexamethasone, cisplatin, cytarabine; A(N)CVB=doxorubicin or mitoxantrone, cyclophosphamide, vindesine, bleomycin; DCV=dacarbazine, cisplatin, vinblastine; IL-2=interleukin-2; IFNa=interferon alfa; Tgb/CsA= antithymocyte globulin, rabbit, cyclosporine; Dec=decitabine; Pac=paclitaxel; MAID=mesna, doxorubicin, ifosfamide, dacarbazine; IA=ifosfamide, doxorubicin.

3Listed under source as high risk chemotherapy regimen (Risk of development of febrile neutropenia >20%)