

**Clinical Pharmacy Program Guidelines for Colony Stimulating Factors- ARIZONA**

Program	Prior Authorization
Medication	<b>Preferred Products:</b> Neupogen (filgrastim, G-CSF), Neulasta (pegfilgrastim, G-CSF), Neulasta Onpro (pegfilgrastim G-CSF), Leukine (sargramostim, GM-CSF), Zarxio (filgrastim, G-CSF), Granix (tbo-filgrastim, G-CSF)

**1. Background:**

**Drug Name: Neulasta (pegfilgrastim, G-CSF)**

**Indications**

**Febrile Neutropenia (FN), Prophylaxis**

Indicated to decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of FN.

**Drug Name: Leukine (sargramostim, GM-CSF)**

**Indications**

**Patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy**

Indicated for use following induction chemotherapy in older adults with AML to shorten time to neutrophil recovery and reduce the incidence of severe and life-threatening infections and infections resulting in death. The safety and efficacy of Leukine have not been assessed in patients with AML under 55 years of age.

**Bone marrow transplant (BMT) - Leukine use in myeloid reconstitution after autologous BMT**

Indicated for acceleration of myeloid recovery in patients with non-Hodgkin’s lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin’s disease undergoing autologous BMT. After autologous BMT in patients with NHL, ALL, or Hodgkin’s disease, Leukine has been found to be safe and effective in accelerating myeloid engraftment, decreasing median duration of antibiotic administration, reducing the median duration of infectious episodes and shortening the median duration of hospitalization. Hematologic response to Leukine can be detected by CBC with differential cell counts performed twice per week.

**Bone marrow transplant (BMT) - Leukine use in myeloid reconstitution after allogeneic BMT**

Indicated for acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors. Leukine has been found to be safe and effective in accelerating myeloid engraftment, reducing the incidence of bacteremia and other culture positive infections, and shortening the median duration of hospitalization.

**Bone marrow transplant (BMT) - Leukine use in BMT failure or engraftment delay**

Indicated in patients who have undergone allogeneic or autologous BMT in whom engraftment is delayed or has failed. Leukine has been found to be safe and effective in prolonging survival of patients who are experiencing graft failure or engraftment delay, in the presence or absence of infection, following autologous or allogeneic BMT. Survival benefit may be relatively greater in those patients who demonstrate one or more of the following characteristics: autologous BMT failure or engraftment delay, no previous total body irradiation, malignancy other than leukemia or a multiple organ failure (MOF) score less than or equal to 2. Hematologic response to Leukine can be detected by CBC with differential performed twice per week.

**Patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy**

Indicated for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment as compared with collection without mobilization. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care. Myeloid reconstitution is further accelerated by administration of Leukine following PBPC transplantation.

**Drug Name: Zarxio (filgrastim-sndz, G-CSF)**

**Indications**

**Febrile Neutropenia (FN), Prophylaxis**

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

**Patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy**

Indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML

**Bone marrow transplant (BMT) - Zarxio use in cancer patients receiving BMT**

Indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation

**Patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy**

Indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis

**Patients with severe chronic neutropenia (SCN)**

Indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (eg, fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

**Drug Name: Neupogen (filgrastim, G-CSF)**

**Indications**

**Febrile Neutropenia (FN), Prophylaxis**

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. A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and twice per week during Neupogen therapy to avoid leukocytosis and to monitor the neutrophil count. In phase 3 clinical studies, Neupogen therapy was discontinued when the absolute neutrophil count (ANC) was greater than or equal to 10,000/mm<sup>3</sup> after the expected chemotherapy-induced nadir.

**Patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy**

Indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML.

**Bone marrow transplant (BMT) - Neupogen use in cancer patients receiving BMT**

Indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation. It is recommended that CBCs and platelet counts be obtained at a minimum of 3 times per week following marrow infusion to monitor the recovery of marrow reconstitution.

**Patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy**

Indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care.

**Patients with severe chronic neutropenia (SCN)**

Indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. It is essential that serial

CBCs with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of Neupogen therapy. The use of Neupogen prior to confirmation of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

### **Off Label Uses**

#### **HIV-related neutropenia**

Has been prescribed for HIV-related neutropenia.

#### **Hepatitis-C Interferon induced neutropenia**

Neupogen has been prescribed for interferon-induced neutropenia in Hepatitis C virus infected patients

**Drug Name: Granix (tbo-filgrastim, G-CSF)**

### **Indications**

#### **Febrile Neutropenia (FN), prophylaxis**

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.

## **2. Coverage Criteria:**

### **A. Bone Marrow/Stem Cell Transplant**

1. **Neupogen, Leukine, Zarxio** will be approved based on **all** of the following criteria:

a. **One** of the following:

(1) Patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by autologous or allogeneic BMT

**-OR-**

(2) For mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis

**-OR-**

(3) For peripheral stem cell transplant (PSCT) patients who have received myeloablative chemotherapy

**-AND-**

- b. Prescribed by or in consultation with a hematologist/oncologist

**Authorization will be issued for 3 months or duration of therapy.**

**B. AML Induction or Consolidation Therapy**

One of the following:

- 1. **Neupogen or Zarxio** will be approved based on **all** of the following criteria:

- a. For patients with AML following induction or consolidation chemotherapy

**-AND-**

- b. Prescribed by or in consultation with a hematologist/oncologist

**-OR-**

- 2. **Leukine** will be approved based on **all** of the following criteria:

- a. For patients with AML following induction or consolidation chemotherapy

**-AND-**

- b. Prescribed by or in consultation with a hematologist/oncologist

**-AND-**

- c. Age greater than or equal to 55 years.

**Authorization will be issued for 3 months or duration of therapy.**

**C. Neutropenia Associated with Cancer Chemotherapy –Dose Dense Chemotherapy**

- 1. **Neulasta, Neulasta Onpro, Neupogen, Leukine, Zarxio** will be approved based on **all** of the following criteria:

- a. **One** of the following:

- (1) Patient is receiving National Cancer Institute's Breast Intergroup, INT C9741 dose dense chemotherapy protocol for primary breast cancer

**-OR-**

- (2) Patient is receiving a dose-dense chemotherapy regimen for which the incidence of FN is unknown

**-AND-**

- b. Prescribed by or in consultation with a hematologist/oncologist

**Authorization will be issued for 3 months or duration of therapy.**

**D. Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia (FN)**

1. **Neulasta, Neulasta Onpro, Neupogen, Zarxio, Granix** will be approved based on **all** of the following criteria:

- a. **One** of the following:

- (1) Patient receiving chemotherapy regimens associated with greater than 20% incidence of FN

**-OR-**

- (2) **Both** of the following:

- (a) Patient receiving chemotherapy regimen associated with 10-20% incidence of FN
- (b) One or more risk factors associated with chemotherapy-induced infection, FN, or neutropenia

**-AND-**

- b. Prescribed by or in consultation with a hematologist/oncologist

**Authorization will be issued for 3 months or duration of therapy.**

**E. Secondary Prophylaxis of Febrile Neutropenia (FN)**

1. **Neulasta, Neulasta Onpro, Neupogen, Zarxio, Granix** will be approved based on **all** of the following criteria:

- a. For patients receiving myelosuppressive anti-cancer drugs associated with neutropenia (ANC less than or equal to 500 cells/mm<sup>3</sup>)

**-AND-**

- b. Patients with a history of FN during a previous course of chemotherapy

**-AND-**

- c. Prescribed by or in consultation with a hematologist/oncologist

**Authorization will be issued for 3 months or duration of therapy.**

**F. Treatment of Febrile Neutropenia (FN) (off-label)**

1. **Neulasta, Neulasta Onpro, Neupogen, Leukine, or Zarxio** will be approved based on **all** of the following criteria:

- a. For patients receiving myelosuppressive anti-cancer drugs associated with neutropenia (ANC less than or equal to 500 cells/mm<sup>3</sup>)

**-AND-**

- b. Patients with FN at high risk for infection-associated complications

**-AND-**

- c. Prescribed by or in consultation with a hematologist/oncologist

**Authorization will be issued for 1 month.**

**G. Severe Chronic Neutropenia (SCN)**

1. **Neupogen or Zarxio** will be approved based on **all** of the following criteria:

- a. For patients with SCN (ie, congenital, cyclic, and idiopathic neutropenias with chronic ANC less than or equal to 500 cells/mm<sup>3</sup>)

**-AND-**

- b. Prescribed by or in consultation with a hematologist/oncologist

**Authorization will be issued for 12 months.**

**H. HIV-Related Neutropenia (off-label)**

1. **Neupogen, Leukine or Zarxio** will be approved based on **all** of the following criteria:

a. Patient is infected with HIV virus

**-AND-**

b. ANC less than or equal to 1,000 cells/mm<sup>3</sup>

**-AND-**

c. Prescribed by or in consultation with one of the following:

- Hematologist/oncologist
- Infectious disease specialist

**Authorization will be issued for 6 months.**

**I. Hepatitis C Treatment Related Neutropenia (off-label)**

1. **Neupogen or Zarxio** will be approved based on **all** of the following criteria:

a. **One** of the following:

(1) **All** of the following:

- (a) Patient infected with hepatitis C virus
- (b) Patient is undergoing treatment with Peg-Intron (peginterferon alfa-2b) or Pegasys (peginterferon alfa-2a)
- (c) Neutropenia (ANC less than or equal to 500 cells/mm<sup>3</sup>) after dose reduction of Peg-Intron or Pegasys

**-OR-**

(2) **Both** of the following:

- (a) Patients who experience interferon-induced neutropenia (ANC less than or equal to 500 cells/mm<sup>3</sup>) due to treatment with Peg-Intron (peginterferon alfa-2b) or Pegasys (peginterferon alfa-2a)

**-AND-**

(b) **One** of the following:



- i. Patient with HIV co-infection
- ii. Status post liver transplant
- iii. Patient with established cirrhosis

**-AND-**

- b. Prescribed by or in consultation with a hematologist/oncologist, gastroenterologist, or infectious disease specialist

**Authorization will be issued for 12 months.**

- A. Currently there is no information available about the effect of longer acting pegylated G-CSF in patients with myeloid leukemias, therefore pegylated G-CSF should not be used in such patients outside of clinical trials. [17]
- B. The safety and efficacy of Leukine in AML induction or consolidation in adults younger than 55 years old have not been established in clinical trials. [3]
- C. Per hematology/oncology consultant and member of P&T, most cycles of induction or consolidation chemotherapy last ~ 1 month, but patients who complete therapy typically receive 1 induction and 2-3 consolidations, so re-approval would need to occur every month.
- D. The safety and efficacy of pegylated G-CSF has not been fully established in the setting of dose-dense chemotherapy. [17]
- E. Per hematology/oncology consultant and member of P&T in general, dose-dense regimens require growth factor support for chemotherapy administration. [16] Also, Neulasta is commonly used to support dose dense regimens in current community practice. It would be reasonable to allow Neulasta use [in the INT C9741 Protocol] and to broaden its use for other forms of dose dense chemotherapy.
- F. The product information for both PEG-Intron and Pegasys recommends dose reduction in patients with neutropenia with an ANC level < 750 cells/mm<sup>3</sup>. [22, 23]
- G. Per GI consultant and member of P&T, his medical group of practicing hepatologists recommends Neupogen for a special subpopulation of patients with HIV infection, status post liver transplant, or established cirrhosis who experience interferon-induced neutropenia (ANC less than or equal to 500 cells/mm<sup>3</sup>) due to treatment with Peg-Intron or Pegasys.
- H. Guidelines issued by the U.S. Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) recommend for HIV-related neutropenia, the length of therapy with G-CSF and GM-CSF is 2-4 weeks. [15]
- I. Note: This list is NOT inclusive of all chemotherapy regimens with a high risk of FN.
- J. Note: This list is NOT inclusive of all chemotherapy regimens with an intermediate risk of FN.

- K. Risk factors are based on provider information, not the list in the table below. Examples of risk factors may include (but are NOT limited to): Risk factors associated with chemotherapy-induced infection, FN, or neutropenia • Age > 65 years [16, 17] • History of extensive prior chemotherapy or radiation therapy including large radiation ports [16, 17] • Previous episodes of FN [16, 17] • Administration of combined chemoradiotherapy [17] • Pre-existing neutropenia or bone marrow involvement with tumor [16, 17] • Pre-existing conditions [16] • Neutropenia • Active infection/open wounds • Recent surgery • Poor performance status [16, 17] • Poor renal function [16] • Liver dysfunction [16] • Poor nutritional status [17] • More advanced cancer [17] • Hypotension and multiorgan dysfunction (Sepsis syndrome) [16, 17] • Pneumonia [16] • Invasive fungal infection [16, 17] • Other clinically documented infections [16] • Hospitalization at the time of fever [16] • Anticipated prolonged (> 10 days) and profound neutropenia (< 100/mm<sup>3</sup>) [17] • Uncontrolled primary disease [17] • Other serious comorbidities [17]
- L. Note: This list is NOT all inclusive: See Table 5 in Background section

## Clinical Practice Guidelines

### National Comprehensive Cancer Network (NCCN) (2012) [11, 16]

Patient risk factors, intent of therapy, and the chemotherapy regimen may be evaluated to assess the risk of a patient developing FN. The prophylactic use of CSFs with concurrent chemotherapy or radiotherapy is not recommended. Additionally, chemotherapy dose reduction or a chemotherapy regimen change may be warranted if a patient experiences FN despite receiving a CSF unless patient survival chances could be affected.

#### Patients at high risk of FN:

NCCN recommends the routine use of CSFs for high risk (> 20%) patients to prevent the development of FN in patients receiving treatment with curative intent, to prolong survival, or to manage symptoms.

The guidelines recognize a variety of special circumstances in which patients with relatively non-myelosuppressive chemotherapy regimens may nonetheless be at high risk of FN due to bone marrow compromise or comorbidity. In addition to the risk of the chemotherapy regimen, the following constitute patient risk factors for developing FN:

- Older patient, notably greater than or equal to 65 years old
- History of previous chemotherapy or radiation therapy
- Pre-existing neutropenia or bone marrow involvement with tumor
- Pre-existing conditions
- Neutropenia

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- Infection/open wounds
- Recent surgery
- Poor performance status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin

#### Patients at intermediate risk of FN:

CSFs may be considered in patients with intermediate risk (10-20%). In all three categories of treatment intent, the guidelines recommend individualized consideration of CSF use based on physician-patient discussion of the risk-benefit ratio of the likelihood of developing FN, the potential consequences of a neutropenic event and the implications of reduced chemotherapy dose delivery. When the intent of chemotherapy is designed to prolong survival or for symptom management, the use of CSF is a difficult decision and requires careful discussion between the physician and patient. If patient risk factors determine the risk, CSF is reasonable. If the risk is due to the chemotherapy regimen, other alternatives such as use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

#### Patients at low risk of FN:

Routine use of CSFs is not considered cost-effective and alternative treatment options are appropriate for patients at low risk for FN (< 10% risk). However, CSFs may be considered if the patient is receiving curative or adjuvant treatment and is at significant risk for serious medical consequences of FN, including death.

#### CSF use for the treatment of FN

There is little evidence to support the use of CSFs as an adjunct to antibiotic therapy. Adjunctive therapy with CSFs may be considered in neutropenic patients at risk for poor clinical outcome or serious infectious complications, such as patient with:

- Advanced age (older than 65 years)
- Fever at hospitalization
- Invasive fungal infections
- Pneumonia
- Other clinically documented infections

- Sepsis syndrome
- Severe (ANC less than 100/mm<sup>3</sup>) or anticipated prolonged (> 10 days) neutropenia
- Prior episode of FN

Patients who have received prophylactic pegfilgrastim should not receive additional CSF. Additionally, there is no evidence to support the use of pegfilgrastim for the treatment of FN.

### American Society of Clinical Oncology (ASCO) (2006) [17]

**Table 6. Summary of ASCO recommendations for use of CSF treatment**

Primary Prophylaxis	General Circumstances	Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For “dose dense” regimens CSFs are required and recommended. Clinical trial data support the use of CSF when the risk of FN is in the range of greater than or equal to 20%. In the absence of special circumstances, most commonly used regimens have risks of FN of < 20%. In making the decision to use prophylactic CSF or not, oncologists should consider not only the optimal chemotherapy regimen but also the individual patient risk factors and the intention of treatment, that is, curative, prolongation of life, or symptom control and palliation. Examples of appropriate use in the curative setting include adjuvant treatment of early-stage breast cancer with more intensive regimens such as TAC* or FEC100** or the use of CHOP <sup>†</sup> or CHOP-like regimens in older patients with aggressive NHL.
	Special Circumstances	Clinicians may occasionally be faced with patients who might benefit from relatively non-myelosuppressive chemotherapy but who have potential risk factors for FN or infection because of bone marrow compromise or comorbidity. It is possible that primary CSF administration may be

		<p>exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications even though the data supporting such use are not conclusive. Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age &gt; 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; bone marrow involvement by tumor producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations primary prophylaxis with CSF is often appropriate even with regimens with FN rates of &lt; 20%. The special circumstances have always been part of ASCO's CSF guidelines, in recognition that there are patient factors that predict for the rate and severity of FN. These special circumstances have been maintained from previous versions of the guideline. The rate at which the use of CSFs should be considered has changed from 40% to 20%, consistent with the new evidence that demonstrates efficacy in reducing FN rates when the risk is approximately 20%.</p>
Secondary Prophylaxis		<p>Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.</p>
	Patients with afebrile neutropenia	<p>CSFs should not be routinely used for patients with neutropenia who are afebrile.</p>
Therapeutic use of	Patients with febrile	<p>CSFs should not be routinely used as</p>

CSFs	neutropenia	adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 x 10 <sup>9</sup> /L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.
Use of CSFs to increase dose intensity or dose density		Use of CSFs allows a modest to moderate increase in dose-density and/or dose-intensity of chemotherapy regimens. Available data would suggest a survival benefit from the use of dose-dense (but not dose-intense) regimens with CSF support in a few specific settings (e.g., node-positive breast cancer, SCLC, and NHL). However, additional data in these settings are needed and these results cannot be generalized to other disease settings and regimens absent specific trials. Dose-dense regimens should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data.
Use of CSFs as adjuncts to progenitor cell transplantation		Administration of CSFs to mobilize PBPC often in conjunction with chemotherapy and their administration after autologous, but not allogeneic, PBPC transplant is the current standard of care.
Use of CSFs for patients with leukemia or MDS	Initial or repeat induction chemotherapy (AML)	Several studies have shown that CSF administration can produce modest decreases in the duration of neutropenia when begun shortly after completion of the initial induction chemotherapy. Beneficial effects on end points such as duration of hospitalization and incidence of severe infections have been variable and modest. CSF use following initial induction

		therapy is reasonable, although there has been no favorable impact on remission rate, remission duration or survival. Patients > 55 years of age may be most likely to benefit from CSF use.
	CSF for priming effects (AML)	Use of CSFs for priming effects is not recommended.
	Consolidation chemotherapy in AML	CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive post remission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission than for patients receiving initial induction therapy. There is no effect on the duration of complete response or overall survival. There is, as yet, no information about the effect of longer acting, pegylated CSFs in patients with myeloid leukemias and they should not be used in such patients outside of clinical trials.
	MDS	CSFs can increase the ANC in neutropenic patients with MDS. Data supporting the routine long-term continuous use of CSFs in these patients are lacking. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection.
	ALL	CSFs are recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post remission course, thus shortening the duration of neutropenia of < 1,000/mm <sup>3</sup> by approximately one week. There are less consistent effects on the incidence and duration of hospitalization and the acquisition of serious infections. Although there was a trend for improved CR rates in one large study, particularly in older adults, there was no prolongation of disease-free or overall survival in any of

		<p>the trials. G-CSF can be given together with the continued corticosteroid/antimetabolite therapy, which is a feature of many ALL regimens, without evidence that such concurrent therapy prolongs the myelosuppressive effects of the chemotherapy. As in AML, it is unknown from the published data whether the CSFs significantly accelerate recovery to neutrophil counts of 100 – 200/mm<sup>3</sup>. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from the hospital. The use of G-CSF for children with ALL was associated with small benefits in days of antibiotics or in-hospital days, although a small amount of additional costs was incurred, after taking into consideration the costs of the CSFs. Cost estimates of CSFs for adults with ALL have not been reported.</p>
	<p>Leukemia in relapse</p>	<p>CSFs should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia. Because of the relatively low response rate in AML patients with relapsed or refractory disease clinicians may be faced with the difficult dilemma of whether the persistence of leukemia after chemotherapy is a consequence of drug resistance or a stimulatory effect of the CSF. Although drug resistance is the most likely cause of treatment failure, it is sometimes necessary to stop the CSF and observe the patient for a few days to be certain.</p>
<p>Use of CSFs in patients receiving radiation therapy</p>		<p>CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSFs may be considered in patients receiving radiation therapy alone if prolonged delays</p>



		secondary to neutropenia are expected.
Use of CSFs in older patients		Prophylactic CSF for patients with lymphoma aged 65 and older treated with curative chemotherapy (CHOP <sup>†</sup> or more aggressive regimens) should be given to reduce the incidence of FN and infections.
Use of CSFs in pediatric patients		The use of G-CSF in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of G-CSF is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly, the use of G-CSF for secondary prophylaxis or for therapy should be limited to high-risk patients. However, the potential risk for secondary myeloid leukemia or MDS associated with G-CSF represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the specific use of G-CSF in children with ALL should be considered carefully.

\*TAC = docetaxel, doxorubicin, cyclophosphamide

\*\*FEC 100 = 5-fluorouracil, epirubicin, cyclophosphamide

<sup>†</sup>CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone

### **American Gastroenterological Association (AGA) (2006) [24]**

The American Gastroenterological Association's Medical Position Statement on the Management of Hepatitis C recommends that for the management of neutropenia associated with interferon, dose reduction suffices and the addition of G-CSF is generally not recommended, although it may be considered in individual cases of severe neutropenia

### **Centers for Disease Control, National Institutes of Health, and the Infectious Disease Society of America (2009) [39]**

An absolute neutrophil count that is depressed because of HIV disease or drug therapy is associated with an increased risk for bacterial infections, including pneumonia. To reduce the risk for such bacterial infections, health-care providers might consider taking steps to reverse neutropenia, either by stopping myelosuppressive drugs or by administering granulocyte-colony

stimulating factor (G-CSF).

**Table 2. Intergroup C9741 Protocol [19]**

Regimen	Drugs	G-CSF
Sequential	Doxorubicin q2 weeks x4 cycles, then paclitaxel q2 weeks x4 cycles, then cyclophosphamide q2 weeks x 4cycles	Days 3 to 10 of each cycle
Concurrent	Doxorubicin + cyclophosphamide q2 weeks x4 cycles, then paclitaxel q2 weeks x4 cycles	Days 3 to 10 of each cycle

**Table 3. Examples of chemotherapy regimens with a high risk of FN (> 20%) [16]**

Cancer	Regimen
Bladder	<ul style="list-style-type: none"> <li>GC (methotrexate, vinblastine, doxorubicin, cisplatin)<sup>17</sup></li> <li>MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)</li> </ul>
Breast <sup>16, 18, 26</sup>	<ul style="list-style-type: none"> <li>Docetaxel + trastuzumab (metastatic or relapsed)</li> <li>Dose dense AC→T (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)</li> <li>AT (doxorubicin, paclitaxel) (metastatic or relapsed)</li> <li>AT (doxorubicin, docetaxel) (metastatic or relapsed)</li> <li>TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)</li> <li>FEC100 (5-fluorouracil, epirubicin, cyclophosphamide)<sup>17</sup></li> </ul>
Esophageal and Gastric	<ul style="list-style-type: none"> <li>DCF (docetaxel, cisplatin, fluorouracil)</li> </ul>
Hodgkin Lymphoma	<ul style="list-style-type: none"> <li>BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)</li> </ul>
Germ cell	<ul style="list-style-type: none"> <li>VeIP (vinblastine, ifosfamide, cisplatin)<sup>17</sup></li> </ul>
Non-Hodgkin's Lymphoma (NHL) <sup>16, 27</sup>	<ul style="list-style-type: none"> <li>CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab) (CLL with del(17p), relapse/refractory)</li> <li>ICE (ifosfamide, carboplatin, etoposide) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphomas, second line, salvage)</li> <li>RICE (rituximab, ifosfamide, carboplatin, etoposide)</li> <li>CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone)</li> <li>MINE (mesna, ifosfamide, novantrone, and etoposide) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphomas, second line, refractory)</li> <li>VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin)<sup>17</sup></li> <li>DHAP (dexamethasone, cisplatin, cytarabine) (Peripheral T-cell Lymphomas, Diffuse Large B-Cell Lymphoma, second</li> </ul>

	line) <ul style="list-style-type: none"> <li>• ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphoma, second line, recurrent)</li> <li>• HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)</li> </ul>
Ovarian	<ul style="list-style-type: none"> <li>• Topotecan</li> <li>• Paclitaxel</li> <li>• Docetaxel</li> </ul>
Sarcoma	<ul style="list-style-type: none"> <li>• MAID (mesna, doxorubicin, ifosfamide, dacarbazine)</li> <li>• Doxorubicin</li> </ul>
Small Cell Lung	<ul style="list-style-type: none"> <li>• Topotecan</li> <li>• CAV (cyclophosphamide, doxorubicin, vincristine)<sup>17</sup></li> </ul>
Testicular	<ul style="list-style-type: none"> <li>• VIP (etoposide, ifosfamide, cisplatin)</li> <li>• VeIP (vinblastine, ifosfamide, cisplatin)</li> <li>• BEP (bleomycin, etoposide, cisplatin)</li> <li>• TIP (paclitaxel, ifosfamide, cisplatin)</li> </ul>
Melanoma	<ul style="list-style-type: none"> <li>• Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)</li> <li>• Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)</li> </ul>
Multiple Myeloma	<ul style="list-style-type: none"> <li>• Modified HyperCVAD</li> </ul>
Myelodysplastic syndrome	<ul style="list-style-type: none"> <li>• Antithymocyte globulin, rabbit/cyclosporine</li> <li>• Decitabine</li> </ul>
Kidney	<ul style="list-style-type: none"> <li>• Doxorubicin/gemcitabine</li> </ul>

**Table 4. Examples of chemotherapy regimens with an intermediate risk of FN (10-20%) [16]**

<b>Cancer</b>	<b>Regimen</b>
Occult Primary-Adenocarcinoma	<ul style="list-style-type: none"> <li>• Gemcitabine, docetaxel</li> </ul>
Breast cancer	<ul style="list-style-type: none"> <li>• Docetaxel every 21 days</li> <li>• Epirubicin (adjuvant)</li> <li>• Epirubicin + sequential cyclophosphamide + methotrexate + 5-fluorouracil (adjuvant)</li> <li>• CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)</li> <li>• AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)</li> <li>• AC + sequential docetaxel + trastuzumab (adjuvant)</li> <li>• FEC (fluorouracil, epirubicin, cyclophosphamide)</li> </ul>

	<ul style="list-style-type: none"> <li>+ sequential docetaxel</li> <li>• Paclitaxel every 21 days (metastatic or relapsed)</li> <li>• Vinblastine (metastatic or relapsed)</li> </ul>
Cervical	<ul style="list-style-type: none"> <li>• Cisplatin + topotecan (recurrent or metastatic)</li> <li>• Topotecan (recurrent or metastatic)</li> <li>• Irinotecan (recurrent or metastatic)</li> </ul>
Hodgkin's disease	<ul style="list-style-type: none"> <li>• ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)</li> <li>• Stanford V (mechlorethamine, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)</li> </ul>
Colon	<ul style="list-style-type: none"> <li>• FOLFOX (fluorouracil, leucovorin, oxaliplatin)</li> </ul>
NHL	<ul style="list-style-type: none"> <li>• EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt's lymphoma, recurrent)</li> <li>• EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, Diffuse Large B-Cell Lymphoma, recurrent)</li> <li>• ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)</li> <li>• GDP (gemcitabine, dexamethasone, cisplatin) (Peripheral T-cell Lymphomas, Diffuse Large B-Cell Lymphoma, second line)</li> <li>• GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (Diffuse Large B-Cell Lymphoma, second line)</li> <li>• FM (fludarabine, mitoxantrone)</li> <li>• CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) including regimens with pegylated liposomal doxorubicin or mitoxantrone substituted for doxorubicin</li> </ul>
Non-small cell lung	<ul style="list-style-type: none"> <li>• Cisplatin/paclitaxel (adjuvant, advanced/metastatic)</li> <li>• Cisplatin/vinorelbine (adjuvant, advanced/metastatic)</li> <li>• Cisplatin/docetaxel (adjuvant, advanced/metastatic)</li> <li>• Cisplatin/irinotecan (advanced/metastatic)</li> <li>• Cisplatin/etoposide (adjuvant, advanced/metastatic)</li> <li>• Carboplatin/paclitaxel (adjuvant, advanced/metastatic)</li> <li>• Docetaxel (advanced/metastatic)</li> </ul>

Ovarian	• Carboplatin/docetaxel
Prostate	• Cabazitaxel
Testicular	• Etoposide/cisplatin
Esophageal and Gastric	• Irinotecan/cisplatin • Epirubicin/cisplatin/5-fluorouracil • Epirubicin/cisplatin/capecitabine
Small cell lung	• Etoposide/carboplatin
Uterine	• Docetaxel (uterine sarcoma, advanced or metastatic)

**Table 5. Examples of FDA-approved chemotherapeutic agents with dose-limiting myelosuppression**

<b>Generic Name</b>	<b>Brand Name</b>
Busulfan	Busulfex <sup>®</sup> , Myleran <sup>®</sup>
Carboplatin	Paraplatin <sup>®</sup>
Carmustine (BCNU)	BiCNU <sup>®</sup> , Gliadel <sup>®</sup>
Chlorambucil	Leukeran <sup>®</sup>
Cladribine	Luestatin <sup>®</sup>
Cyclophosphamide	Cytosan <sup>®</sup>
Cytarabine	N/A
Dacarbazine (DTIC)	DTIC-Dome <sup>®</sup>
Dactinomycin	Actinomycin D <sup>®</sup> , Cosmegen <sup>®</sup>
Daunorubicin	Cerubidine <sup>®</sup>
Daunorubicin Liposomal	DaunoXome <sup>®</sup>
Doxorubicin	Adriamycin PFS <sup>®</sup> , Adriamycin RDF <sup>®</sup> , Adriamycin <sup>®</sup>
Doxorubicin Liposomal	Doxil <sup>®</sup>
Etoposide	Etopophos <sup>®</sup> , Toposar <sup>®</sup> , VePesid <sup>®</sup>
Fluorouracil (5-FU)	Adrucil <sup>®</sup> , Efudex <sup>®</sup> , Fluoroplex <sup>®</sup>
Floxuridine	FUDR <sup>®</sup>
Fludarabine	Fludara <sup>®</sup>
Hydroxyurea	Droxia <sup>®</sup> , Hydrea <sup>®</sup>
Ifosfamide/Mesna	Ifex <sup>®</sup> , Mesnex <sup>®</sup>
Lomustine (CCNU)	CeeNU <sup>®</sup>
Mechlorethamine (Nitrogen Mustard)	Mustargen <sup>®</sup>
Melphalan	Alkeran <sup>®</sup>
Mercaptopurine (6-MP)	Purinethol <sup>®</sup>
Methotrexate	Rheumatrex <sup>®</sup> , Trexall <sup>®</sup>
Mitomycin	N/A
Mitoxantrone	Novantrone <sup>®</sup>
Paclitaxel	Onxol <sup>™</sup> , Taxol <sup>®</sup>
Procarbazine	Matulane <sup>®</sup>

Teniposide	Vumon <sup>®</sup>
Thioguanine (6-TG)	Tabloid <sup>®</sup>
Thiotepa	Thiotepa <sup>®</sup>
Vinblastine	N/A
Vincristine	Vincasar <sup>®</sup> PFS
Vinorelbine	Navelbine <sup>®</sup>

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Program	Prior Authorization - Neulasta (pegfilgrastim, G-CSF), Leukine (sargramostim, GM-CSF), Zarxio ((filgrastim, G-CSF), Neupogen (filgrastim, G-CSF), Granix (tbo-filgrastim, G-CSF)
<b>Change Control</b>	
Date	Change
August 2017	New policy specific to Arizona.
12/2017	Added Neulasta Onpro to medications section and throughout criteria as a preferred product. Updated references.