



**PHARMACY PRIOR AUTHORIZATION**  
**Clinical Guideline - Colony Stimulating Factors**  
**Neupogen® (filgrastim; G-CSF), Neulasta® (peg-filgrastim; G-CSF),**  
**Neumega® (oprelvekin; rh-IL-11)**

### Indications

#### Neupogen (FDA approved):

##### For the treatment of neutropenia:

- for congenital, cyclic, or idiopathic neutropenia
- in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation

##### For chemotherapy-induced neutropenia prophylaxis in patients receiving myelosuppressive chemotherapy:

- Primary prophylaxis in patients receiving chemotherapy regimens with an expected incidence of febrile neutropenia  $\geq 20\%$
- Secondary prophylaxis in patients with a previous episode of febrile neutropenia

##### For peripheral blood stem cell (PBSC) mobilization prior to and during leukapheresis in cancer patients preparing to undergo bone marrow ablation

#### Other indications: (non-FDA approved):

- For the treatment of HIV-induced, or drug therapy-induced neutropenia
- Treatment of neutropenia in patients with myelodysplastic syndrome
- For the adjunctive treatment of aplastic anemia (with cyclosporine, Thymoglobulin, and/or steroids)
- As primary prophylaxis for febrile neutropenia and to reduce the time to neutrophil recovery and duration of febrile neutropenia following induction or consolidation chemotherapy for acute lymphoid leukemia (ALL)
- For decreasing the period of neutropenia following reinfusion of peripheral blood stem cells (PBSCs)

#### Neulasta:

**For prophylaxis of chemotherapy-induced neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with an expected incidence of febrile neutropenia  $\geq 17\%$**

#### Neumega:

**For the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia.**

### Dosage Forms

**Neupogen:** single-use vials: 300mcg/ml, 480mcg/1.6ml; prefilled syringes: 300mcg/0.5ml, 480mcg/0.8ml

**Neulasta:** 6mg/0.6ml syringe

**Neumega:** 5mg vial (powder for injection)

### Dosage

**\*Dosing and duration of therapy varies by product and indication. Please refer to individual product monographs.**

- **Neupogen:** *Adults and children:* 5-10mcg/kg IV/SC once daily
- **Neulasta:**
  - *Adults and adolescents  $\geq 45$  kg:* 6 mg SC once per chemotherapy cycle (of 14 days or longer).
  - *Adolescents, children, or infants  $< 45$  kg:* Not recommended.
- **Neumega:**
  - *Adults:* 50mcg/kg SC once daily.
  - *Adjust dose for renal dysfunction:* for  $ClCr < 30$  ml/min, reduce dosage to 25mcg SC once daily.

### Authorization Guidelines



**Prior authorization personnel will review the request for prior authorization and apply the clinical guidelines to assess the medical necessity of the request for a prescription for Neupogen, Neulasta, Neumega. If the guidelines are met, the reviewer will prior authorize the prescription. If the guidelines are not met, the prior authorization request will be referred to a physician reviewer for a medical necessity determination. Such a request for prior authorization will be approved when, in the professional judgment of the physician reviewer, the services are medically necessary to meet the medical needs of the recipient.**

**Note:** Neutropenia is defined as an absolute neutrophil count (ANC) less than 500, or an ANC of 1000 with an expected drop to <500 within the next 48 hours

**ANC = % neutrophils x WBC. Example: WBC 2.4, neutrophils 47% = 2400 x 0.47 = ANC 1128**

**FOR PATIENTS WHO MEET ALL THE FOLLOWING:**

**All Agents:**

- **Medical records to support medication will be administered in provider's office. Self-administered injectables are available through the Delaware Medicaid pharmacy benefit. Members should be directed to Delaware retail pharmacies with prescriptions to obtain these drugs.**

**Neupogen:**

- No *E. coli* protein hypersensitivity (patients who may have reacted to *E. coli* asparaginase)
- Timing restriction: Is not administered in the period between 24 hours before and 24 hours after administration of cytotoxic chemotherapy. Concurrent use with mitomycin C, antimetabolites (e.g., 5-fluorouracil, cytosine arabinoside) or chemotherapeutic agents that have a delayed myelosuppressive effect (e.g., nitrosoureas) has not been evaluated and should be avoided.
- Not receiving concurrent chemotherapy and radiation therapy
- Prescribed by hematologist and/or oncologist per associated diagnosis/indication
- Medical records documenting medically accepted indication/diagnosis (see "Indications" section)
- Additional documentation based on medically accepted indication/diagnosis:
  - Primary prophylaxis of chemotherapy-induced neutropenia
    - Chemotherapy regimen has an expected incidence of febrile neutropenia  $\geq 20\%$  (see chart under "Additional Information"), and/or
    - Member is high-risk for neutropenic complications (e.g., Age >65, Pre-existing Neutropenia or tumor involvement in the bone marrow, Infection, Renal or liver impairment, Other serious co-morbidities. See "Additional Information")
  - Secondary prophylaxis of chemotherapy-induced neutropenia
    - Medical records to support febrile neutropenia with a previous cycle of chemotherapy

**Neulasta:**

- No *E. coli* protein hypersensitivity (patients who may have reacted to *E. coli* asparaginase)
- Patient is an adults or adolescent and weighs  $\geq 45$  kg
- Timing restriction: Is not administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy. Concurrent use with radiation therapy, mitomycin C, antimetabolites (e.g., 5-fluorouracil, cytosine arabinoside) or chemotherapeutic agents that have a delayed myelosuppressive effect (e.g., nitrosoureas) has not been evaluated and should be avoided.
- Prescribed by hematologist and/or oncologist per associated diagnosis/indication
- Medical records documenting medically accepted indication/diagnosis (see "Indications" section)
- Additional documentation based on medically accepted indication/diagnosis:
  - Primary prophylaxis of chemotherapy-induced neutropenia
    - Chemotherapy regimens has an expected incidence of febrile neutropenia  $\geq 17\%$  and chemotherapy cycle of >14 days, and/or
    - Member is high-risk for neutropenic complications (e.g., Age >65, Pre-existing Neutropenia, Infection/open wounds, Renal impairment, Liver dysfunction, Poor



nutritional status, Other serious co-morbidities. See "Additional Information")

**Neumega:**

- No oprelvekin hypersensitivity
- Timing restriction: Neumega treatment begins 6-12 hours after the completion of chemotherapy. (Maximum treatment duration: 21 days. Discontinue treatment at least 2 days prior to next chemotherapy cycle.)
- Not used after myeloablative therapy
- Not used for and has not been evaluated for use for chemotherapy regimens >5 days duration, or regimens with delayed myelosuppression
- Not used for and has not been studied for myeloid malignancies (e.g., leukemia, multiple myeloma)
- Is 12 years of age and older
- Prescribed by hematologist and/or oncologist per associated diagnosis/indication
- Medical records documenting use for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia.
- Baseline platelet count

**FOR NON-FDA APPROVED INDICATIONS (see individual agents listed below)** (e.g., MDS, HIV, aplastic anemia, drug-induced neutropenia):

**Neupogen, Neulasta**

- Medical records documenting medically accepted indication/diagnosis
- Medical literature from peer-reviewed journals with safety, efficacy and dosing information for the intended use
- Recent ANC <500 if used for treatment of neutropenia
- For treatment of Hepatitis C patients with documented drug-induced neutropenia: high risk groups only—advanced cirrhosis, pre- and post-liver transplant, HIV/HCV coinfection, or if patient does not respond to a dosage adjustment

**Neumega**

- Medical records documenting medically accepted indication/diagnosis
- Medical literature from peer-reviewed journals with safety, efficacy and dosing information for the intended use
- Baseline platelet count

## Prior Authorization Requirements

### Initial Approval

**FDA- Approved indications**

- Chemotherapy-induced neutropenia (primary or secondary prophylaxis): Approve per cycle of chemotherapy: up to a 10 day supply for Neupogen, or one 6mg dose of Neulasta (include refills if number of cycles is provided)
- Treatment of Neutropenia (e.g., congenital, cyclic, or idiopathic, or after chemo + BMT): Approve x 3 months

**For non-FDA approved indications** (e.g., myelodysplastic syndrome, HIV drug-induced neutropenia):

- Short-term therapy: approve per cycle of chemotherapy, or 4 weeks at a time
- Long-term therapy: approve x 6 months

### Renewal

**Chemotherapy-induced neutropenia** (primary or secondary prophylaxis):

- Recent ANC showing a response to therapy
- Approve per cycle of chemotherapy: up to a 10 day supply for Neupogen, or one 6mg dose of Neulasta
- Include refills if number of cycles is provided

**All other indications:**

- Recent ANC
- Recent platelet counts
- Approve up to 1 year, depending on the indication



**Additional Information**

**Note:** Neutropenia is defined as an absolute neutrophil count (ANC) less than 500, or an ANC of 1000 with an expected drop to <500 within the next 48 hours

**ANC = % neutrophils x WBC. Example: WBC 2.4, neutrophils 47% = 2400 x 0.47 = ANC 1128**

**Prevention of Febrile Neutropenia**

**Determining the risk of febrile neutropenia:**

- **Chemotherapy Regimen** - The aggressiveness of the chemotherapy regimen can be taken into account by giving to each individual drug a score (ranging from 0 to 4), according to its expected hematological toxicity. For combination drug regimens, the regimen’s score is calculated by taking the mean of the individual agent’s weights. (Example: vinblastine + carboplatin = 5 ÷ 2= 2.5). A score ≥3 is considered high risk for neutropenia. If the score is <3 it is considered lower risk and you should check for other risk factors before determining the final risk.

**Useful tables:**

**Table 1: Individual scores of chemotherapy agents**

Score 0	Score 1	Score 2	Score 3	Score 4
Asparaginase	6-Thioguanin	Actinomycin D	2-CDA	Adriamycin >90 mg/m <sup>2</sup>
Bleomycin	5-fluorouracil	Dacarbazine	Adriamycin ≤90 mg/m <sup>2</sup>	Busulfan
Farnesyl	Cisplatin	Fludarabin	Alimta	Carmustine
Rituximab	Gemcitabine	Mechloorethamin	Amsacrin	Cyclophosphamide >1 g/m <sup>2</sup>
Methotrexate + leucovorin	Chlorambucil	Melphalan ≤70 mg/m <sup>2</sup>	Bendamustin	Cytarabin (Ara C) >2 g/m <sup>2</sup>
STI 571	Vindesine	Mitomycin C	Camptothecin	Docetaxel
Thalidomide	Vinorelbin	Mitoxantron	Carboplatin	Etoposide >100 mg/m <sup>2</sup>
Tretinoide	Thiotepa	Purinethol	Cyclophosphamide ≤1 g/m <sup>2</sup>	Gemtuzumab
Bortezomib	Hydroxyurea	Procarbazine	Cytarabin (Ara C) ≤2 g/m <sup>2</sup>	Idarubicin
Vincristine		Temozolomid	Daunorubicin	Ifosfamide >9 g/m <sup>2</sup>
Campath		Vinblastine	Epirubicin	Melphalan >70 mg/m <sup>2</sup>
			Etoposide ≤100 mg/m <sup>2</sup>	Topotecan
			Ifosfamide ≤9 g/m <sup>2</sup>	
			Oxaliplatin	
			Teniposid	

A weight (0–4) is assigned to each drug according to its expected frequency of severe neutropenia (0 unusual, 1 very rare, 2 rare, 3 frequent, 4 very frequent). This weight was determined using data on the basis of single drug therapy.

M. Moreau, J. Klastersky, A. Schwarzbald, et al. A general chemotherapy myelotoxicity score to predict febrile neutropenia in hematological malignancies. Ann Oncol 2009; 20:513-519

**Table 2: Chemotherapy score linked to the degree of induced neutropenia**

Score 0	Bleomycin, asparaginase, leucovorin
Score 1	5-fluorouracil, cisplatin, fludarabin
Score 2	Melphalan, mitomycin C, methotrexate, carmustin, busulfan, vinblastin, gemcitabine, vinorelbin, mitoxantrone, raltitrexed, vindesin, dacarbazin
Score 3	Doxorubicin, carboplatin, cyclophosphamide, epirubicin, ifosfamide, cytarabin, idarubicin, oxaliplatin
Score 4	Paclitaxel, docetaxel, etoposid, irinotecan, topotecan, HD doxorubicin, HD cyclophosphamide, HD cisplatin, HD ifosfamide, HD etoposid, HD cytarabin

Score 0, no neutropenia; score 1, mild neutropenia; score 2, moderate neutropenia; score 3, intermediate neutropenia; score 4, severe neutropenia.

High-dose chemotherapy doses (HD): doxorubicin >90 mg/m<sup>2</sup>, cisplatin >100 mg/m<sup>2</sup>, cyclophosphamide >1000 mg/m<sup>2</sup>, ifosfamide

>9000 mg/m<sup>2</sup>, etoposide >500 mg/m<sup>2</sup> and cytarabine >1000 mg/m<sup>2</sup>.

Lalami Y, et al. Can we predict the duration of chemotherapy-induced neutropenia in febrile neutropenic patients, focusing on regimen-specific risk factors? A retrospective analysis. *Ann Oncol* 2006;17:507-14

- **Patient Specific Risk Factors** – In addition to the risk of the chemotherapy regimen these factors need to be considered when evaluating a patient's overall risk for febrile neutropenia. The MASCC calculator can be found at <http://www.qxmd.com/calculate-online/hematology/febrile-neutropenia-mascc>. A score of < 21 indicates high risk for febrile neutropenia complications
  - **Type of cancer** (hematologic malignancies – leukemia, lymphoma)
  - **Pre-existing conditions:**
    - Age >65
    - Previous chemotherapy or radiation therapy
    - Advanced disease or uncontrolled cancer
    - Pre-existing neutropenia, anemia or other cytopenias, or bone marrow involvement of tumor
    - Active Infection/open wounds, pneumonia, sepsis
    - Poor performance status (e.g., poor nutritional status, low albumin)
    - Renal impairment (GFR<30 or age >65 and elevated creatinine)
    - Liver dysfunction (elevated bilirubin, alkaline phosphatase)
    - Other serious co-morbidities (heart disease, hypertension, COPD)
    - Previous episodes of FN

**Treatment of Febrile Neutropenia Secondary to Chemotherapy** – There is less evidence supporting therapeutic use of CSFs for febrile neutropenia as an adjunctive to antibiotics. For patients who have not received prophylactic CSFs, CSFs should be considered if patient has risk factors for infection-associated complications (e.g., prolonged hospitalization and increased mortality):

- Age >65 years
- Sepsis syndrome
- Severe neutropenia (ANC<100), or anticipated prolonged (>10 days) neutropenia
- Pneumonia, or other clinically documented infection
- Invasive fungal infection or other clinically-documented infections
- Hospitalized at the time of development of fever
- Prior episode of febrile neutropenia

#### **Neutropenia secondary to hepatitis C treatment (peg-IFN):**

- Incidence of neutropenia (defined as ANC 1500 or less) was reported in 18-20% of patients in large clinical trials
- Despite the decline in neutrophil count, serious infections are uncommon
- High risk patients may benefit from CSFs: advanced cirrhosis, pre- and post-liver transplant and HIV/HCV coinfection
- Data is lacking to support routine use of CSFs for neutropenia in hepatitis C
- Dosage reduction is recommended as first-line treatment:
  - **For Pegasys:** The manufacturer recommends a dosage adjustment to 135mcg per week (25% dosage reduction) for ANC <750 and suspend treatment for ANC <500. Resume Pegasys 90mcg per week once ANC >1000.
  - **For Peg-Intron:** The manufacturer recommends a 50% dosage reduction for WBC <1500, ANC<750 or platelet count < 80,000. The manufacturer recommends the drug be permanently discontinued for WBC <1000, ANC<500, or platelet count <50,000

#### **Adherence is more important than dose reduction in achieving Sustained virologic response (SVR)**

- Patients receiving at least 80% of either total drug dose or of treatment duration, achieve the highest sustained virologic response.
- Generally, ribavirin dose reductions of up to 40% do not appear to compromise SVR. SVR is higher if

RBV is >10.6mg/kg/day (more than 800mg for a 75kg person)

- Reducing the dose of peg-IFN does not appear to significantly impact either EVR or SVR

#### From e-Medicine :

Growth factors such as granulocyte-stimulating factor and erythropoietin are frequently used to counteract the adverse hematological effects of IFN and ribavirin, respectively. Despite the encouraging results reported by Afdhal et al in 2004 and Van Thiel et al in 1995, cost-effectiveness data supporting their routine use as a means of avoiding IFN and ribavirin dose reductions are insufficient.

#### **Aetna considers treatment of interferon-induced neutropenia to be experimental and investigational.**

Although G-CSF shows tremendous promise for managing hematological side effects of combination therapy for HCV, and potentially enhancing adherence, further research is need to clarify the safety, effectiveness, and cost-effectiveness of growth factors in the management of patients with chronic HCV.

### References

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