## 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 ≥ 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 ≥ 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.

**Leukine:**
- For the treatment of neutropenia:
  - following induction chemotherapy in older adults (>55 yrs old) with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death
- For acceleration of myeloid recovery:
  - in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL), and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT).
  - in patients undergoing allogeneic BMT from HLA-matched related donors.
For patients who have undergone allogeneic or autologous bone marrow transplantation (BMT) in whom engraftment is delayed or has failed

For peripheral blood stem cell (PBSC) mobilization prior to apheresis (i.e., leukapheresis) in cancer patients undergoing bone marrow ablation

Other indications: (non-FDA approved):
- For the treatment of neutropenia:
  - For the treatment of HIV-induced, or drug therapy-induced neutropenia
  - In patients with myelodysplastic syndrome
  - For chemotherapy-induced neutropenia prophylaxis in patients receiving myelosuppressive chemotherapy in patients with malignancies other than acute myelogenous leukemia
- For the treatment of severe aplastic anemia
- For the adjuvant treatment of malignant melanoma following surgery for stage III or IV melanoma who are at high-risk for recurrence
- For the treatment of human immunodeficiency virus (HIV) infection

### 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)
- **Leukine:** 500mcg/ml 1ml vial, 250mcg 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 ≥ 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 CICr<30 ml/min, reduce dosage to 25mcg SC once daily.
- **Leukine:**
  - *Adults and children*: 250 mcg/m² SC or IV over 2 hours once daily
  - *Doses have ranged from 125—500 mcg/m²/day*

### 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, Leukine. 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:**
- **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

Additional documentation based on medically accepted indication/diagnosis:
- **Primary prophylaxis** of chemotherapy-induced neutropenia
  - Chemotherapy regimen has an expected incidence of febrile neutropenia ≥ 20% (see chart under “Additional Information”), 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)
- **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
- 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
- Additional documentation based on medically accepted indication/diagnosis:
  - **Primary prophylaxis** of chemotherapy-induced neutropenia
    - Chemotherapy regimen has an expected incidence of febrile neutropenia ≥ 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)

**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 medically accepted indication/diagnosis
- 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

**Leukine:**
- No benzyl alcohol or yeast hypersensitivity
- Timing restriction: Is not administered in the period between 24 hours before and 24 hours after
administration of cytotoxic chemotherapy
- Not being used for neonates
- No evidence of excessive leukemic blasts (≥10%) in bone marrow or peripheral blood (could act as a growth factor for myeloid leukemia)
- Not used in patients receiving concurrent chemotherapy and radiation therapy
- Prescribed by hematologist and/or oncologist per associated diagnosis/indication
- Medical records documenting medically accepted indication/diagnosis

FOR NON-FDA APPROVED INDICATIONS (e.g., MDS, HIV, aplastic anemia, drug-induced neutropenia):

**Neupogen, Neulasta, Leukine**
- 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

**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

## References

4. Millman Care Guidelines, 11th Edition. Available at:


### Primary Reference Policy

#### 7600.12 Non-Formulary Management

### 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**

**High Risk patients - Increased risk of febrile neutropenia (FN) and/or complications from neutropenia**

- Type of cancer (Small cell lung cancer, Lymphoma, Breast cancer)
- Type of chemotherapy (myelosuppresive, more than 2 agents, dose-intensive)
- Pre-existing conditons:
  - Age >65
  - Pre-existing Neutropenia, or other cytopenias (e.g., due to bone marrow involvement of tumor)
  - Active Infection/open wounds
  - Renal impairment (GFR<30 or age >65 and elevated creatinine)
  - Liver dysfunction (elevated bilirubin, alkaline phosphatase)
  - Poor nutritional status
  - Other serious co-morbidities
  - Previous episodes of FN
  - History of previous chemotherapy or radiation therapy
Treatment of Febrile Neutropenia Secondary to Chemotherapy – Clinical benefit has not been proven unless patient is high-risk for infection associated complications (e.g., prolonged hospitalization and increased mortality):

- Age >65 years
- ANC<100
- Pneumonia
- Hypotension
- Multiorgan dysfunction (e.g., cardiac, pulmonary, hepatic, renal disease)
- Invasive fungal infection
- Hospitalized at the time of development of fever

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 (SVR 75%).
- Generally, dose reductions of up to 40% do not appear to compromise SVR (SVR drops to 67%)
- 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 needed to clarify the safety, effectiveness, and cost-effectiveness of growth factors in the management of patients with chronic HCV.