I. Policy

FDA approved colony-stimulating factors (G-CSF or GM-CSF) may be considered medically necessary for the following FDA-approved indications:

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA-approved Indications</th>
</tr>
</thead>
</table>
| Filgrastim (G-CSF) (Neupogen®) | ▪ Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever  
  ▪ Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)  
  ▪ Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT)  
  ▪ Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis  
  ▪ Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia  
  ▪ Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) |
| Filgrastim-sndz (G-CSF) (Zarxio®) | ▪ Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid  
  ▪ Mobilize autologous hematopoietic progenitor cells into the peripheral blood |
<table>
<thead>
<tr>
<th>Policy Title</th>
<th>Colony-Stimulating Factors (G-CSF and GM-CSF) and Stem Cell Mobilizers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Policy Number</strong></td>
<td>MP-2.101</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegfilgrastim (G-CSF) (Neulasta®)</td>
<td>- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.</td>
</tr>
<tr>
<td>Tbo-filgrastim (G-CSF) (Granix®)</td>
<td>- Reduction in 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.</td>
</tr>
<tr>
<td>Sargramostim (GM-CSF) (Leukine®)</td>
<td>- For use following induction chemotherapy in older adult patients (e.g., &gt; 55 years of age) 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. The safety and efficacy of Leukine® has not been assessed in patients with AML under 55 years of age.</td>
</tr>
</tbody>
</table>

Colony-Stimulating Factors (G-CSF or GM-CSF) are considered investigational for all other indications. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these drugs for any other indications.

**Stem Cell Mobilizers**

Plerixafor (Mozobil®) may be considered medically necessary when used in combination with granulocyte-colony stimulating factors (G-CSF and GM-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin’s lymphoma and multiple myeloma. Plerixafor (Mozobil®) may be
considered **medically necessary** for treatment of the off-label indication of Hodgkin’s lymphoma.

Plerixafor (Mozobil ®) is considered **investigational** for all other indications as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this drug for any other indications.

**Cross-reference:**
- MP-2.004 Donor Lymphocyte Infusion for Hematologic Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant
- MP-2.103 Off-Label Use of Medications
- MP-9.001 Placental Umbilical Cord Blood as a Source of Stem Cells
- MP-9.038 Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
- MP-9.039 Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia
- MP-9.040 Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
- MP-9.042 Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphoma
- MP-9.043 Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma
- MP-9.044 Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- MP-9.045 Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis
- MP-9.046 Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia
- MP-9.047 Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer
- MP-9.048 Hematopoietic Stem-Cell Transplantation Miscellaneous Solid Tumors in Adults
- MP-9.050 Hematopoietic Stem-Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- MP-9.052 Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors
- MP-9.053 Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases
- MP-9.054 Hematopoietic Stem-Cell Transplantation for Solid Tumors of Children
- MP-9.055 Allogeneic HSCT for Genetic Diseases and Acquired Anemias
- MP-9.056 Allogeneic Stem-Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

**II. PRODUCT VARIATIONS**

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

**FEP PPO**

* For Leukine refer to FEP Medical Policy Manual 5.10.08
* For Neupogen refer to FEP Medical Policy Manual MP-5.10.10
* For Granix refer to FEP Medical Policy Manual 5.10.16
* For Mozobil - The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered
investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

The FEP Medical Policy manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

Bone marrow produces different types of cells, including red and white blood cells. Certain white blood cells (WBCs), known as granulocytes and macrophages, are part of the immune system that the body uses to fight infections. Types of granulocytes include neutrophils, eosinophils, and basophils. Neutropenia is a condition in which there is a lower-than-normal number of neutrophils (i.e. less than 1500 to 2000 per microliter). Causes of neutropenia include chemotherapy treatment and congenital or idiopathic conditions. Neutropenia can put a patient at risk for life-threatening infections.

Under certain circumstances, the bone marrow may not be able to produce enough white blood cells to fight infections. Granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF and GM-CSF) stimulate the bone marrow to produce white blood cells.

Examples of G-CSFs include Filgrastim (Neupogen), pegfilgrastim (Neulasta), tbo-filgrastim (Granix), and filgrastim sndz (Zarxio). Pegfilgrastim (Neulasta) is a long-acting form of filgrastim. An example of a GM-CSFs is Sargramostim (Leukine). These drugs are artificially produced and must be given by injection or intravenous infusion until patients are able to produce adequate WBCs on their own.

Filgrastim (Neupogen) has been approved by the by the U.S. Food and Drug Administration (FDA) for the following indications: cancer patients receiving myelosuppressive chemotherapy or bone marrow transplant, patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, patients undergoing peripheral blood progenitor cell collection/therapy and patients with severe chronic neutropenia (e.g. congenital, cyclic, or idiopathic). Filgrastim is administered by daily subcutaneous injections. The dose and schedule varies by clinical condition.

Pegfilgrastim (Neulasta) has been approved by the FDA to reduce the incidence of infection associated with chemotherapy. The recommended dose is a single subcutaneous injection administered once per chemotherapy cycle. Since the drug is administered at the onset of a treatment cycle, it remains in the blood while the patient is neutropenic and before complications begin.

Sargramostim (Leukine) has been approved by the FDA for the following indications: following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery, use in mobilization and following transplantation of autologous peripheral blood progenitor cells, use in myeloid reconstitution after autologous bone marrow transplantation, use in myeloid reconstitution after allogeneic bone marrow
transplantation, and use in bone marrow transplantation failure or engraftment delay. Filgrastim is administered by daily subcutaneous injections. The dose and schedule varies by clinical condition.

Tbo-filgrastim (Granix) is approved by the FDA for the following indication: for reduction in 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. The recommended dose is 5 mcg/kg per day administered as a subcutaneous injection, administered no earlier than 24 hours following myelosuppressive chemotherapy.

Filgrastim-sndz (Zarxio) produced by Sandoz, is a close copy of the existing medication Neupogen, made by Amgen. It was approved in Europe in 2009 as Zarzio but has not been used in the United States, in part because no regulatory pathway existed to bring biosimilars — approximate copies of drugs in a class known as biologics — to market. But in January an expert panel unanimously recommended that the F.D.A. approve it. Zarxio has been approved by the FDA for the following indications: to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever, to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML), 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 bone marrow transplantation (BMT), to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis, and to reduce the incidence and duration of sequelae of severe neutropenia (e.g. fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. The dose and schedule varies by clinical condition.

Plerixafor (Mozobil)) is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin’s lymphoma and multiple myeloma. Under certain circumstances, the bone marrow may not be able to produce enough white blood cells to fight infections. Granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF and GM-CSF) stimulate the bone marrow to produce white blood cells.

Mozobil treatment should begin after the patient has received G-CSF once daily for four days. Mozobil is then administered approximately 11 hours prior to the initiation of apheresis for up to four consecutive days. Mozobil is administered by subcutaneous injection based on 0.24 mg/kg body weight. In patients with renal impairment, the dose of Mozobil should be decreased by one-third to 0.16/kg.

**IV. RATIONALE**
Filgrastim (Neupogen®)

Patients with Cancer Receiving Myelosuppressive Chemotherapy

The safety and efficacy of NEUPOGEN to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).

In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21 day cycles. Patients were randomized to receive NEUPOGEN (n=99) at a dose of 230 mcg/m² (4 to 8 mcg/kg/day) or placebo (n=111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease. The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an ANC < 1000/mm³ and temperature > 38.2°C. Treatment with NEUPOGEN resulted in a clinically and statistically significant reduction in the incidence of infection as manifested by febrile neutropenia, 40% for NEUPOGEN-treated patients and 76% for placebo-treated patients (p < 0.001). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm³); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of NEUPOGEN to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, de novo AML (Study 4).

In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous NEUPOGEN (n=259) at a dose of 5 mcg/kg/day or placebo (n=262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥ 1000/mm³ for 3 consecutive days or ≥ 10,000/mm³ for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white blood cell count (65% < 25,000/mm³ and 27% > 100,000/mm³); 29% unfavorable cytogenetics.

The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count <500/mm³. Treatment with NEUPOGEN resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, NEUPOGEN-treated
patients 14 days, placebo-treated patients 19 days (p = 0.0001: difference of 5 days (95% CI: -6.0, -4.0)). There was a reduction in the median duration of intravenous antibiotic use, NEUPOGEN-treated patients: 15 days versus placebo treated patients: 18.5 days; a reduction in the median duration of hospitalization, NEUPOGEN-treated patients: 20 days versus placebo-treated patients: 25 days. There were no statistically significant differences between the NEUPOGEN and the placebo groups in complete remission rate (69% - NEUPOGEN, 68% - placebo), median time to progression of all randomized patients (165 days - NEUPOGEN, 186 days - placebo), or median overall survival (380 days -NEUPOGEN, 425 days - placebo).

Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of NEUPOGEN to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of NEUPOGEN to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo controlled trial (Study 10).

In Study 6 patients with Hodgkin’s disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU (“CVP”), and patients with non-Hodgkin’s lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan (“BEAM”). There were 54 patients randomized 1:1:1 to control, NEUPOGEN 10 mcg/kg/day, and NEUPOGEN 30 mcg/kg/day as a 24 hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin’s disease and 31% non-Hodgkin’s lymphoma.

The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm3) occurred in the NEUPOGEN-treated groups versus the control group (23 days in the control group' 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group 

In Study 9, patients with Hodgkin’s disease and non-Hodgkin’s lymphoma received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU (“CVP”). There were 43 evaluable patients randomized to continuous subcutaneous infusion NEUPOGEN 10 mcg/kg/day (n=19), NEUPOGEN 30 mcg/kg/day (n=10) and no treatment (n=14) starting the day after marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin’s disease and 72% non-Hodgkin’s lymphoma.

The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm3) in the NEUPOGEN treated groups versus the control group (21.5 days in the control group versus 10 days in the NEUPOGEN treated groups, p < 0.001). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the NEUPOGEN-treated groups, p < 0.0001).
In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive NEUPOGEN 300 mcg/m2/day (n=33) or placebo (n=37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group’ p < 0.001) and time to recovery of ANC to ≥ 500/mm3 (21 days in the control group and 16 days in the treatment group, p < 0.001).

Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The safety and efficacy of NEUPOGEN to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using NEUPOGEN mobilized autologous peripheral blood progenitor cells to autologous bone marrow (Study 11). Patients in all these trials underwent a similar mobilization/collection regimen: NEUPOGEN was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of NEUPOGEN ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using NEUPOGEN mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm3 by day 28. In clinical trials of NEUPOGEN for the mobilization of hematopoietic progenitor cells, NEUPOGEN was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm3) was reached. The rate of engraftment of these cells in the absence of NEUPOGEN post transplantation has not been studied.

Study 11 was a randomized, unblinded study of patients with Hodgkin’s disease or non-Hodgkin’s lymphoma undergoing myeloablative chemotherapy, 27 patients received NEUPOGEN-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan (“BEAM”). Patients received daily NEUPOGEN 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin’s disease and 43% non-Hodgkin’s lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to NEUPOGEN-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs 10 days).

Patients with Severe Chronic Neutropenia

The safety and efficacy of NEUPOGEN to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric
patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with severe neutropenia (Study 7). Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < 500/mm³ on three occasions during a 6 month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < 500/mm³ per cycle. In addition patients must have experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4 month observation period followed by NEUPOGEN treatment or immediate NEUPOGEN treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia. NEUPOGEN was administered subcutaneously. The dose of NEUPOGEN was determined by the category of neutropenia. Initial dose of NEUPOGEN:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response. The main efficacy endpoint was response to NEUPOGEN treatment. ANC response from baseline (<500/mm³) was defined as follows:

- Complete response: median ANC > 1500/mm³
- Partial response: median ANC ≥ 500/mm³ and ≤ 1500/mm³ with a minimum increase of 100%
- No response: median ANC < 500/mm³

There were 112 of 123 patients who demonstrated a complete or partial response to NEUPOGEN treatment. Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving NEUPOGEN of the following parameters:

- incidence of infection
- incidence of fever
- duration of fever
- incidence, duration, and severity of oropharyngeal ulcers
- number of days of antibiotic use

The incidence for each of these 5 clinical parameters was lower in the NEUPOGEN arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although NEUPOGEN substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.
Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Efficacy studies of NEUPOGEN could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting the use of NEUPOGEN for other approved indications associated with extrapolating animal efficacy data to humans, the selection of human dose for NEUPOGEN is aimed at providing exposures to filgrastim that exceed those observed in animal efficacy studies. The 10 mcg/kg daily dose is selected for humans exposed to myelosuppressive doses of radiation because the exposure associated with such a dose is expected to exceed the exposure associated with a 10 mcg/kg dose in non-human primates. The safety of NEUPOGEN at a daily dose of 10 mcg/kg has been assessed on the basis of clinical experience in approved indications.

The efficacy of NEUPOGEN was studied in a randomized, blinded, placebo-controlled study in a nonhuman primate model of radiation injury. The planned sample size was 62 animals, but the study was stopped at the interim analysis with 46 animals because efficacy was established. Rhesus macaques were randomized to a control (n = 22) or treated (n = 24) group. Animals were exposed to total body irradiation of 7.4 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Starting on day 1 after irradiation, animals received daily subcutaneous injections of placebo (5% dextrose in water) or filgrastim (10 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC ≥ 1,000/mm3 for 3 consecutive days, or ANC ≥ 10,000/mm3 for more than 2 consecutive days within study day 1 to 5, or ANC ≥ 10,000/mm3 any time after study day 5. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Filgrastim significantly (at 0.023 level of significance) reduced 60-day mortality in the irradiated nonhuman primates: 21% mortality (5/24) in the filgrastim group compared to 59% mortality (13/22) in the control group.

Pegfilgrastim (Neulasta®)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n =
Table 1. Adverse Reactions With > 5% Higher Incidence in Neulasta Patients Compared to Placebo in Study 3

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo (N= 461)</th>
<th>Neulasta 6 mg SC on Day 2 (N= 467)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>26%</td>
<td>31%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Bone pain and pain in extremity occurred at a higher incidence in Neulasta-treated patients as compared with placebo-treated patients.

Sargramostim (Leukine®)
During the consolidation phase of treatment, Leukine did not shorten the median time to recovery of ANC to 500/mm³ (13 days) or 1000/mm³ (14.5 days) compared to placebo. There were no significant differences in time to platelet and RBC transfusion independence.

The incidence of severe infections and deaths associated with infections was significantly reduced in patients who received Leukine. During induction or consolidation, 27 of 52 patients receiving Leukine and 35 of 47 patients receiving placebo had at least one grade 3, 4 or 5 infection (p=0.02). Twenty-five patients receiving Leukine and 30 patients receiving placebo experiencing severe and fatal infections during induction only. There were significantly fewer deaths from infectious causes in the Leukine arm (3 versus 11, p=0.02). The majority of deaths in the placebo group were associated with fungal infections with pneumonia as the primary infection.

Disease outcomes were not adversely affected by the use of Leukine. The proportion of patients achieving complete remission (CR) was higher in the LEUKINE group (69% as compared to 55% for the placebo group), but the difference was not significant (p=0.21). There was no significant difference in relapse rates; 12 of 36 patients who received LEUKINE and five of 26 patients who received placebo relapsed within 180 days of documented CR (p=0.26). The overall median survival was 378 days for patients receiving LEUKINE and 268 days for those on placebo (p=0.17). The study was not sized to assess the impact of LEUKINE treatment on response or survival.

Mobilization and Engraftment of PBPC

A retrospective review was conducted of data from patients with cancer undergoing collection of peripheral blood progenitor cells (PBPC) at a single transplant center. Mobilization of PBPC and myeloid reconstitution post-transplant were compared between four groups of patients (n=196) receiving Leukine for mobilization and a historical control group who did not receive any
mobilization treatment [progenitor cells collected by leukapheresis without mobilization (n=100)]. Sequential cohorts received Leukine. The cohorts differed by dose (125 or 250 mcg/m2/day), route (IV over 24 hours or SC) and use of Leukine post-transplant. Leukaphereses were initiated for all mobilization groups after the WBC reached 10,000/mm3. Leukaphereses continued until both a minimum number of mononucleated cells (MNC) were collected (6.5 or 8.0 × 10^8/kg body weight) and a minimum number of phereses (5–8) were performed. Both minimum requirements varied by treatment cohort and planned conditioning regimen. If subjects failed to reach a WBC of 10,000 cells/mm3 by day five, another cytokine was substituted for Leukine; these subjects were all successfully leukapheresed and transplanted. The most marked mobilization and post-transplant effects were seen in patients administered the higher dose of Leukine (250 mcg/m2) either IV (n=63) or SC (n=41).

PBPCs from patients treated at the 250 mcg/m2/day dose had significantly higher number of granulocyte-macrophage colony-forming units (CFU-GM) than those collected without mobilization. The mean value after thawing was 11.41 × 10^4 CFU-GM/kg for all Leukine-mobilized patients, compared to 0.96 × 10^4/kg for the non-mobilized group. A similar difference was observed in the mean number of erythrocyte burst-forming units (BFU-E) collected (23.96 × 10^4/kg for patients mobilized with 250 mcg/m2 doses of Leukine administered SC vs. 1.63 × 10^4/kg for non-mobilized patients).

After transplantation, mobilized subjects had shorter times to myeloid engraftment and fewer days between transplantation and the last platelet transfusion compared to non-mobilized subjects. Neutrophil recovery (ANC >500/mm3) was more rapid in patients administered Leukine following PBPC transplantation with Leukine-mobilized cells (see Table 2). Mobilized patients also had fewer days to the last platelet transfusion and last RBC transfusion, and a shorter duration of hospitalization than did non-mobilized subjects.

During the consolidation phase of treatment, Leukine did not shorten the median time to recovery of ANC to 500/mm3 (13 days) or 1000/mm3 (14.5 days) compared to placebo. There were no significant differences in time to platelet and RBC transfusion independence.

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survival was 378 days for patients receiving Leukine and 268 days for those on placebo (p=0.17). The study was not sized to assess the impact of Leukine treatment on response or survival.

Mobilization and Engraftment of PBPC

A retrospective review was conducted of data from patients with cancer undergoing collection of peripheral blood progenitor cells (PBPC) at a single transplant center. Mobilization of PBPC and myeloid reconstitution post-transplant were compared between four groups of patients (n=196) receiving Leukine for mobilization and a historical control group who did not receive any mobilization treatment [progenitor cells collected by leukapheresis without mobilization (n=100)]. Sequential cohorts received Leukine. The cohorts differed by dose (125 or 250 mcg/m2/day), route (IV over 24 hours or SC) and use of Leukine post-transplant. Leukaphereses were initiated for all mobilization groups after the WBC reached 10,000/mm3. Leukaphereses continued until both a minimum number of mononucleated cells (MNC) were collected (6.5 or 8.0) or ed cells (MNC) were collected (6.5 or 8.0) were performed. Both minimum requirements varied by treatment cohort and planned conditioning regimen. If subjects failed to reach a WBC of 10,000 cells/mm3 by day five, another cytokine was substituted for Leukine; these subjects were all successfully leukapheresed and transplanted. The most marked mobilization and post-transplant effects were seen in patients administered the higher dose of Leukine (250 mcg/m2) either IV (n=63) or SC (n=41).

PBPCs from patients treated at the 250 mcg/m2/day dose had significantly higher number of granulocyte-macrophage colony-forming units (CFU-GM) than those collected without mobilization. The mean value after thawing was 11.41 e had significantly high Leukine mobilized patients, compared to 0.96 × 104/kg for the non-mobilized group. A similar difference was observed in the mean number of erythrocyte burst-forming units (BFU-E) collected (23.96 × 104/kg for patients mobilized with 250 mcg/m2 doses of Leukine administered SC vs. 1.63 × 104/kg for non-mobilized patients).

After transplantation, mobilized subjects had shorter times to myeloid engraftment and fewer days between transplantation and the last platelet transfusion compared to non-mobilized subjects. Neutrophil recovery (ANC >500/mm3) was more rapid in patients administered Leukine following PBPC transplantation with Leukine-mobilized cells (see Table 2). Mobilized patients also had fewer days to the last platelet transfusion and last RBC transfusion, and a shorter duration of hospitalization than did non-mobilized subjects.
A second retrospective review of data from patients undergoing PBPC at another single transplant center was also conducted. Leukine was given SC at 250 mcg/m2/day once a day (n=10) or twice a day (n=21) until completion of the phereses. Phereses were begun on day 5 of Leukine administration and continued until the targeted MNC count of 9 (n=21) until completion of the phereses. Phereses were ed. -mobilized subjects mobilized subjects red to non-mobilized subj Leukine once or twice a day. The median time to ANC>500/mm3 was 12 days and to platelet recovery (>25,000/mm3) was 23 days.

Survival studies comparing mobilized study patients to the nonmobilized patients and to an autologous historical bone marrow transplant group showed no differences in median survival time.

**Autologous Bone Marrow Transplantation**
Following a dose-ranging Phase I/II trial in patients undergoing autologous BMT for lymphoid malignancies, three single center, and randomized, placebo-controlled and double-blinded studies were conducted to evaluate the safety and efficacy of Leukine for promoting hematopoietic reconstitution following autologous BMT. A total of 128 patients (65 Leukine, 63 placebo) were enrolled in these three studies. The majority of the patients had lymphoid malignancy (87 NHL, 17 ALL), 23 patients had Hodgkin's disease, and one patient had acute myeloblastic leukemia (AML). In 72 patients with NHL or ALL, the bone marrow harvest was purged prior to storage with one of several monoclonal antibodies. No chemical agent was used for *in vitro* treatment of the bone marrow. Preparative regimens in the three studies included cyclophosphamide (total dose 120everal monoclonal antibodies. No chemical agent was used for adrads). Other regimens used in patients with Hodgkin's disease and NHL without radiotherapy consisted of three or more of the following in combination (expressed as total dose): cytosine arabinoside (400 mg/m2) and carmustine (300 mg/m2), cyclophosphamide (140–150 mg/kg), hydroxyurea (4.5 grams/m2) and etoposide (375–450 mg/m2).

Compared to placebo, administration of Leukine in two studies (n=44 and 47) significantly improved the following hematologic and clinical endpoints: time to neutrophil engraftment,
duration of hospitalization and infection experience or antibacterial usage. In the third study (n=37) there was a positive trend toward earlier myeloid engraftment in favor of Leukine. This latter study differed from the other two in having enrolled a large number of patients with Hodgkin's disease who had also received extensive radiation and chemotherapy prior to harvest of autologous bone marrow. A subgroup analysis of the data from all three studies revealed that the median time to engraftment for patients with Hodgkin's disease, regardless of treatment, was six days longer when compared to patients with NHL and ALL, but that the overall beneficial Leukine treatment effect was the same. In the following combined analysis of the three studies, these two subgroups (NHL and ALL vs. Hodgkin's disease) are presented separately.

**Table 3**

<table>
<thead>
<tr>
<th>ANC ≥500/mm³</th>
<th>ANC 1000/mm³</th>
<th>Duration of Hospitalization</th>
<th>Duration of Infection</th>
<th>Duration of Antibacterial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEUKINE (n=54)</td>
<td>18*+ 24*+ 25*</td>
<td>1*</td>
<td>21*</td>
<td></td>
</tr>
<tr>
<td>Placebo (n=50)</td>
<td>24 32 31 4</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The single AML patient was not included.
* p <0.05 Wilcoxon or CMH ridit chi-squared
† p <0.05 Log rank

Patients with Lymphoid Malignancy (Non-Hodgkin's Lymphoma and Acute Lymphoblastic Leukemia)

Myeloid engraftment (absolute neutrophil count [ANC] ≥500 cells/mm³) in 54 patients receiving Leukine was observed 6 days earlier than in 50 patients treated with placebo (see Table 3). Accelerated myeloid engraftment was associated with significant clinical benefits. The median duration of hospitalization was six days shorter for the Leukine group than for the placebo group. Median duration of infectious episodes (defined as fever and neutropenia; or two positive cultures of the same organism; or fever >38°C and one positive blood culture; or clinical evidence of infection) was three days less in the group treated with Leukine. The median duration of antibacterial administration in the post-transplantation period was four days shorter for the patients treated with Leukine than for placebo-treated patients. The study was unable to detect a significant difference between the treatment groups in rate of disease relapse 24 months post-transplantation. As a group, leukemic subjects receiving Leukine derived less benefit than NHL subjects. However, both the leukemic and NHL groups receiving Leukine engrafted earlier than controls.
Patients with Hodgkin's Disease

If patients with Hodgkin's disease are analyzed separately, a trend toward earlier myeloid engraftment is noted. Leukine-treated patients engrafted earlier (by five days) than the placebo-treated patients (p=0.189, Wilcoxon) but the number of patients was small (n=22).

Allogeneic Bone Marrow Transplantation

A multi-center, randomized, placebo-controlled, and double-blinded study was conducted to evaluate the safety and efficacy of Leukine for promoting hematopoietic reconstitution following allogeneic BMT. A total of 109 patients (53 Leukien, 56 placebo) were enrolled in the study. Twenty-three patients (11 Leukine, 12 placebo) were 18 years old or younger. Sixty-seven patients had myeloid malignancies (33 AML, 34 CML), 17 had lymphoid malignancies (12 ALL, 5 NHL), three patients had Hodgkin's disease, six had multiple myeloma, nine had myelodysplastic disease, and seven patients had aplastic anemia. In 22 patients at one of the seven study sites, bone marrow harvests were depleted of T cells. Preparative regimens included cyclophosphamide, busulfan, cytosine arabinoside, etoposide, methotrexate, corticosteroids, and asparaginase. Some patients also received total body, splenic, or testicular irradiation. Primary graft-versus-host disease (GVHD) prophylaxis was cyclosporine A and a corticosteroid.

Accelerated myeloid engraftment was associated with significant laboratory and clinical benefits. Compared to placebo, administration of Leukine significantly improved the following: time to neutrophil engraftment, duration of hospitalization, number of patients with bacteremia and overall incidence of infection (see Table 4).

Table 4

<table>
<thead>
<tr>
<th>Allogeneic BMT: Analysis of Data from Placebo-Controlled Clinical Trial Median Values (days or number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC ≥ 500/mm³</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>LEUKINE (n=53)</td>
</tr>
<tr>
<td>Placebo (n=56)</td>
</tr>
</tbody>
</table>

*p <0.05 generalized Wilcoxon test †p <0.05 simple chi-square test

Median time to myeloid engraftment (ANC ≥ 500 cells/mm³) in 53 patients receiving Leukine was 4 four days less than in 56 patients treated with placebo (see Table 4). The number of patients with bacteremia and infection was significantly lower in the Leukine group compared to the
placebo group (9/53 versus 19/56 and 30/53 versus 42/56, respectively). There were a number of secondary laboratory and clinical endpoints. Of these, only the incidence of severe (grade 3/4) mucositis was significantly improved in the Leukine group (4/53) compared to the placebo group (16/56) at p<0.05. Leukine-treated patients also had a shorter median duration of post-transplant IV antibiotic infusions, and shorter median number of days to last platelet and RBC transfusions compared to placebo patients, but none of these differences reached statistical significance.

**Bone Marrow Transplantation Failure or Engraftment Delay**

A historically-controlled study was conducted in patients experiencing graft failure following allogeneic or autologous BMT to determine whether Leukine improved survival after BMT failure. Three categories of patients were eligible for this study:

1. patients displaying a delay in engraftment (ANC ≤ 100 cells/mm³ by day 28 post-transplantation);
2. patients displaying a delay in engraftment (ANC ≤ 100 cells/mm³ by day 21 post-transplantation) and who had evidence of an active infection; and
3. patients who lost their marrow graft after a transient engraftment (manifested by an average of ANC ≥ 500 cells/mm³ for at least one week followed by loss of engraftment with ANC < 500 cells/mm³ for at least one week beyond day 21 post-transplantation).

A total of 140 eligible patients from 35 institutions were treated with Leukine and evaluated in comparison to 103 historical control patients from a single institution. One hundred sixty-three patients had lymphoid or myeloid leukemia, 24 patients had non-Hodgkin's lymphoma, 19 patients had Hodgkin's disease and 37 patients had other diseases, such as aplastic anemia, myelodysplasia or non-hematologic malignancy. The majority of patients (223 out of 243) had received prior chemotherapy with or without radiotherapy and/or immunotherapy prior to preparation for transplantation.

One hundred day survival was improved in favor of the patients treated with Leukine after graft failure following either autologous or allogeneic BMT. In addition, the median survival was improved by greater than two-fold. The median survival of patients treated with Leukine after autologous failure was 474 days versus 161 days for the historical patients. Similarly, after allogeneic failure, the median survival was 97 days with Leukine treatment and 35 days for the historical controls. Improvement in survival was better in patients with fewer impaired organs.

The MOF score is a simple clinical and laboratory assessment of seven major organ systems: cardiovascular, respiratory, gastrointestinal, hematologic, renal, hepatic and neurologic. Assessment of the MOF score is recommended as an additional method of determining the need to initiate treatment with Leukine in patients with graft failure or delay in engraftment following autologous or allogeneic BMT (see Table 5).
Factors that Contribute to Survival

The probability of survival was relatively greater for patients with any one of the following characteristics: autologous BMT failure or delay in engraftment, exclusion of total body irradiation from the preparative regimen, a non-leukemic malignancy or MOF score ≤ two (zero, one or two dysfunctional organ systems). Leukemic subjects derived less benefit than other subjects.

Tbo-Filgrastim (Granix®)

The efficacy of Granix was evaluated in a multinational, multicenter, randomized and controlled Phase 3 study in 348 chemotherapy-naive patients with high-risk stage II, stage III, or stage IV breast cancer receiving doxorubicin (60 mg/m²) and docetaxel (75 mg/m²) comparing GRANIX to placebo and a non-US-approved filgrastim product as controls. The median age of the patients was 50 years (range 25 to 75 years) with 99% female and 86% Caucasian.

Granix, placebo, and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 10⁶/L after nadir was reached. Granix was superior to placebo in duration of severe neutropenia (DSN) with a statistically significant reduction in DSN (1.1 days vs. 3.8 days, p < 0.0001).

Filgrastim-sndz (Zarxio®)

Patients with Cancer Receiving Myelosuppressive Chemotherapy

The safety and efficacy of filgrastim to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).
In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21 day cycles. Patients were randomized to receive filgrastim (n=99) at a dose of 230 mcg/m2 (4 to 8 mcg/kg/day) or placebo (n=111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease.

The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an ANC <1000/mm3 and temperature > 38.2°C. Treatment with filgrastim resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, 40% for filgrastim-treated patients and 76% for placebo-treated patients (p < 0.001). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm3); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of filgrastim to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, de novo AML (Study 4).

In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous filgrastim (n=259) at a dose of 5 mcg/kg/day or placebo (n=262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥1000/mm3 for 3 consecutive days or ≥ 10,000/mm3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white count (65% - <25,000 /mm3 and 27% > 100,000/mm3); 29% unfavorable cytogenetics. The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm3.

Treatment with filgrastim resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, filgrastim-treated patients 14 days, placebo-treated patients 19 days (p = 0.0001: difference of 5 days (95% CI: -6.0, -4.0)). There was a reduction in the median duration of intravenous antibiotic use, filgrastim treated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, filgrastim-treated patients: 20 days versus placebo-treated patients: 25 days. There were no
statistically significant differences between the filgrastim and the placebo groups in complete remission rate (69% - filgrastim, 68% - placebo), median time to progression of all randomized patients (165 days - filgrastim, 186 days - placebo), or median overall survival (380 days - filgrastim, 425 days - placebo).

Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo controlled trial (Study 10).

In Study 6 patients with Hodgkin’s disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU (“CVP”), and patients with non-Hodgkin’s lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan (“BEAM”). There were 54 patients randomized 1:1:1 to control, filgrastim 10 mcg/kg/day, and filgrastim 30 mcg/kg/day as a 24 hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin’s disease and 31% non-Hodgkin’s lymphoma. The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm3) occurred in the filgrastim-treated groups versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group [11 days in the combined treatment groups, p = 0.004]).

In Study 9, patients with Hodgkin’s disease and non-Hodgkin’s lymphoma received a preparative regimen intravenous cyclophosphamide, etoposide, and BCNU (“CVP”). There were 43 evaluable patients randomized to continuous subcutaneous infusion filgrastim 10 mcg/kg/day (n=19), filgrastim 30 mcg/kg/day (n=10) and no treatment (n=14) starting the day after marrow infusion for maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin’s disease and 72% non-Hodgkin’s lymphoma. The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm3) in the filgrastim-treated groups versus the control group (21.5 days in the control group versus 10 days in the filgrastim-treated groups, p < 0.001). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the filgrastim-treated groups, p < 0.0001).

In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive filgrastim 300 mcg/m2/day (n=33) or placebo (n=37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19
days in the control group and 15 days in the treatment group, p < 0.001) and time to recovery of ANC to ≥ 500/mm³ (21 days in the control group and 16 days in the treatment group, p < 0.001).

**Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy**

The safety and efficacy of filgrastim to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using filgrastim mobilized autologous peripheral blood progenitor cells to autologous bone marrow (Study 11). Patients in all these trials underwent a similar mobilization/collection regimen: filgrastim was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of filgrastim ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using filgrastim mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm³ by day 28. In clinical trials of filgrastim for the mobilization of hematopoietic progenitor cells, filgrastim was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm³) was reached. The rate of engraftment of these cells in the absence of filgrastim post transplantation has not been studied.

Study 11 was a randomized, unblinded study of patients with Hodgkin’s disease or non-Hodgkin’s lymphoma undergoing myeloablative chemotherapy, 27 patients received filgrastim-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan (“BEAM”). Patient received daily filgrastim 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin’s disease and 43% non-Hodgkin’s lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to filgrastim-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs 10 days).

**Patients with Severe Chronic Neutropenia**

The safety and efficacy of filgrastim to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with severe neutropenia (Study 7).

Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < 500/mm³ on three occasions during a 6 month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < 500/mm³ per cycle. In addition patients must have
Medical Policy

<table>
<thead>
<tr>
<th>Policy Title</th>
<th>Colony-Stimulating Factors (G-CSF and GM-CSF) and Stem Cell Mobilizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy Number</td>
<td>MP-2.101</td>
</tr>
</tbody>
</table>

Experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4 month observation period followed by filgrastim treatment or immediate filgrastim treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia. Filgrastim was administered subcutaneously. The dose of filgrastim was determined by the category of neutropenia.

Initial dose of filgrastim:
- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response. The main efficacy endpoint was response to filgrastim treatment. ANC response from baseline (< 500/mm3) was defined as follows:
- Complete response: median ANC > 1500/mm3
- Partial response: median ANC ≥ 500/mm3 and ≤ 1500/mm3 with a minimum increase of 100%
- No response: median ANC < 500/mm3

There were 112 of 123 patients who demonstrated a complete or partial response to filgrastim treatment. Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving filgrastim of the following parameters:
- Incidence of infection
- Incidence of fever
- Duration of fever
- Incidence, duration, and severity of oropharyngeal ulcers
- Number of days of antibiotic use

The incidence for each of these 5 clinical parameters was lower in the filgrastim arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although filgrastim substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.

Plerixafor (Mozobil®)

The efficacy and safety of Mozobil in conjunction with G-CSF in non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) were evaluated in two placebo-controlled studies (Studies 1 and 2). Patients were randomized to receive either Mozobil 0.24 mg/kg or placebo on each evening prior to apheresis. Patients received daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first dose of Mozobil or placebo and on each morning prior to apheresis. Two hundred
and ninety-eight (298) NHL patients were included in the primary efficacy analyses for Study 1. The mean age was 55 years (range 29–75) and 58 years (range 22–75) in the Mozobil and placebo groups, respectively, and 93% of subjects were Caucasian. In study 2, 302 patients with MM were included in the primary efficacy analyses. The mean age (58 years) and age range (28–75) were similar in the Mozobil and placebo groups, and 81% of subjects were Caucasian.

In Study 1, 59% of NHL patients who were mobilized with Mozobil and G-CSF collected ≥ 5 × 10⁶ CD34+ cells/kg from the peripheral blood in four or fewer apheresis sessions, compared with 20% of patients who were mobilized with placebo and G-CSF (p < 0.001). Other CD34+ cell mobilization outcomes showed similar findings (Table 4).

The median number of days to reach blood ≥ 6 CD34+ cells/kg was 3 days for the Mozobil group and not evaluable for the placebo group. Table 5 presents the proportion of patients who achieved ≥ 5 × 10⁶ CD34+ cells/kg by apheresis day.

In Study 2, 72% of MM patients who were mobilized with Mozobil and G-CSF collected t6 CD34+ cells/kg from the peripheral blood in two or fewer apheresis sessions, compared with 34% of patients who were mobilized with placebo and G-CSF (p < 0.001). Other CD34+ cell mobilization outcomes showed similar findings (Table 6).
Table 6: Study 2 Efficacy Results – CD34+ Cell Mobilization in Multiple Myeloma Patients

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>Mozobil® and G-CSF (n = 148)</th>
<th>Placebo and G-CSF (n = 154)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients achieving ≥ 6 x 10^6 cells/kg in ≤ 2 apheresis days</td>
<td>106 (72%)</td>
<td>53 (34%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Patients achieving ≥ 6 x 10^6 cells/kg in ≤ 4 apheresis days</td>
<td>112 (76%)</td>
<td>79 (51%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Patients achieving ≥ 2 x 10^6 cells/kg in ≤ 4 apheresis days</td>
<td>141 (96%)</td>
<td>136 (88%)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

* p-value calculated using Pearson's Chi-Squared test

The median number of days to reach blood ≥ 6 CD34+ cells/kg was 1 day for the Mozobil group and 4 days for the placebo group. Table 7 presents the proportion of patients who achieved ≥ 6 x 10^6 CD34+ cells/kg by apheresis day.

Table 7: Study 2 – Proportion of Patients Who Achieved ≥ 6 x 10^6 CD34+ cells/kg by Apheresis Day in MM Patients

<table>
<thead>
<tr>
<th>Days</th>
<th>Proportion* in Mozobil® and G-CSF (n=144†)</th>
<th>Proportion* in Placebo and G-CSF (n=150†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54.2%</td>
<td>17.3%</td>
</tr>
<tr>
<td>2</td>
<td>77.9%</td>
<td>35.3%</td>
</tr>
<tr>
<td>3</td>
<td>86.8%</td>
<td>48.9%</td>
</tr>
<tr>
<td>4</td>
<td>86.8%</td>
<td>55.9%</td>
</tr>
</tbody>
</table>

* Percents determined by Kaplan Meier method
† n includes all patients who received at least one day of apheresis

Multiple factors can influence time to engraftment and graft durability following stem cell transplantation. For transplanted patients in the Phase 3 studies, time to neutrophil and platelet engraftment and graft durability were similar across the treatment groups.

V. DEFINITIONS

**ALLOGENEIC** refers to having a different genetic constitution but belonging to the same species, i.e., involves a donor and a recipient.

**ALLOGRAFT** refers to transplant tissue obtained from a member of one's own species.
AUTOLOGOUS refers to originating within an individual, i.e., self-donation.

CYTOPENIA is the diminution of cellular elements in blood or other tissue.

MYELOABLATIVE refers to treatment designed to destroy virtually all blood cells and cancer cells.

NEUTROPENIA is the presence of an abnormally small number of neutrophils in the blood, usually less than 1500 to 2000 per microliter.

NEUTROPHIL is a granular white blood cell (WBC), the most common type. It functions in fighting acute infections.

OFF LABEL DRUG USE is the use of a drug to treat a condition for which it has not been approved by the U.S. Food and Drug Administration (FDA), especially when such may relieve unpleasant symptoms or prove compassionate. Drug effects that have been observed but not specifically proven (and for which no application has been made) may be utilized for unproven, or "off-label" uses by licensed medical practitioners.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.
VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary for the above FDA indications:

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1442</td>
<td>Injection, filgrastim (G-CSF), 1 microgram</td>
</tr>
<tr>
<td>J1447</td>
<td>Injection, tbo-filgrastim, 1 microgram</td>
</tr>
<tr>
<td>J2505</td>
<td>Injection, pegfilgrastim, 6 mg</td>
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<tr>
<td>J2562</td>
<td>Injection, plerixafor, 1 mg</td>
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<tr>
<td>J2820</td>
<td>Injection, sargramostim (GM-CSF), 50 mcg</td>
</tr>
<tr>
<td>Q5101</td>
<td>Injection, filgrastim (G-CSF), biosimilar, 1 microgram</td>
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<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B20</td>
<td>Human immunodeficiency virus [HIV] disease</td>
</tr>
<tr>
<td>B25.0</td>
<td>Cytomegaloviral pneumonitis</td>
</tr>
<tr>
<td>B25.1</td>
<td>Cytomegaloviral hepatitis</td>
</tr>
<tr>
<td>B25.2</td>
<td>Cytomegaloviral pancreatitis</td>
</tr>
<tr>
<td>B25.8</td>
<td>Other cytomegaloviral diseases</td>
</tr>
<tr>
<td>B25.9</td>
<td>Cytomegaloviral disease, unspecified</td>
</tr>
<tr>
<td>D46.0</td>
<td>Refractory anemia without ring sideroblasts, so stated</td>
</tr>
<tr>
<td>D46.1</td>
<td>Refractory anemia with ring sideroblasts</td>
</tr>
<tr>
<td>D46.20</td>
<td>Refractory anemia with excess of blasts, unspecified</td>
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<tr>
<td>D46.21</td>
<td>Refractory anemia with excess of blasts 1</td>
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<tr>
<td>D46.4</td>
<td>Refractory anemia, unspecified</td>
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<tr>
<td>D46.9</td>
<td>Myelodysplastic syndrome, unspecified</td>
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<tr>
<td>D46.A</td>
<td>Refractory cytopenia with multilineage dysplasia</td>
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<tr>
<td>D46.B</td>
<td>Refractory cytopenia with multilineage dysplasia and ring sideroblasts</td>
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<tr>
<td>D46.22</td>
<td>Refractory anemia with excess of blasts 2</td>
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<tr>
<td>D46.C</td>
<td>Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality</td>
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<tr>
<td>D46.9</td>
<td>Myelodysplastic syndrome, unspecified</td>
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<tr>
<td>D46.Z</td>
<td>Other myelodysplastic syndromes</td>
</tr>
<tr>
<td>D47.1</td>
<td>Chronic myeloproliferative disease</td>
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</tbody>
</table>
ICD-10-CM Diagnosis Code* | Description
--- | ---
D47.3 | Essential (hemorrhagic) thrombocythemia
D61.9 | Aplastic anemia, unspecified
D70.0 | Congenital agranulocytosis
D70.1 | Agranulocytosis secondary to cancer chemotherapy
D70.2 | Other drug-induced agranulocytosis
D70.3 | Neutropenia due to infection
D70.4 | Cyclic neutropenia
D70.8 | Other neutropenia
D70.9 | Neutropenia, unspecified
K12.31 | Oral mucositis (ulcerative) due to antineoplastic therapy
K12.33 | Oral mucositis (ulcerative) due to radiation
R50.81 | Fever presenting with conditions classified elsewhere
T86.00 | Unspecified complication of bone marrow transplant
T86.01 | Bone marrow transplant rejection
T86.02 | Bone marrow transplant failure
T86.03 | Bone marrow transplant infection
T86.09 | Other complications of bone marrow transplant
Z48.290 | Encounter for aftercare following bone marrow transplant
Z51.11 | Encounter for antineoplastic chemotherapy
Z51.12 | Encounter for antineoplastic immunotherapy
Z52.001 | Unspecified donor, stem cells
Z52.011 | Autologous donor, stem cells
Z52.091 | Other blood donor, stem cells
Z94.81 | Bone marrow transplant status

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES


**MEDICAL POLICY**

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>COLONY-STIMULATING FACTORS (G-CSF AND GM-CSF) AND STEM CELL MOBILIZERS</th>
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<tr>
<td>POLICY NUMBER</td>
<td>MP-2.101</td>
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Plerixafor (Mozobil ®)


X. POLICY HISTORY

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<th>MP 2.101</th>
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<td>CAC 6/28/05</td>
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<td>CAC 1/27/09</td>
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<tr>
<td>CAC 11/24/09</td>
<td>Minor revision adding Plerixafor (Mozobil ®) to the policy.</td>
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<td>CAC 11/30/10</td>
<td>Consensus no change in policy statement. References updated.</td>
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<td>CAC 11/22/11</td>
<td>Consensus review.</td>
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<td>CAC 3/26/13</td>
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<table>
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<tr>
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<tbody>
<tr>
<td>CAC 1/27/15</td>
<td>Consensus review. References updated. Rationale added. No changes to the policy statements. Coding reviewed.</td>
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<td>Minor revision. Filgrastim-sndz (Zarxio) recently FDA-approved added to the policy. Tbo-filgrastim (Granix) also added to the policy. Granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF and GM-CSF) medications were placed in a table and revised to indicate their FDA-approved indications. Background, reference, and rationale update. FEP variation updated. Policy coded.</td>
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<td>2016 coding update; removed end dated code &amp; added new code.</td>
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<tr>
<td>CAC 11/29/16</td>
<td>Consensus review. No change to policy statements. References updated. Coding reviewed. Variation reformatting.</td>
</tr>
</tbody>
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Top

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