MEDICAL MUTUAL®

Drug Policy

Policy:	**201424**	**Initial Effective Date: 10/30/2014**
Code(s):	**HCPCS J1442, Q5101, Q5110**	**Annual Review Date: 08/16/2018**
SUBJECT:	**Colony Stimulating Factors** - Neupogen® (filgrastim) - Nivestym (filgrastim-aafi) - **Zarxio™ (filgrastim-sndz)***	**Last Revised Date: 08/16/2018**

***Zarxio™ (filgrastim-sndz) is the preferred filgrastim product as of November 1, 2018**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

Neupogen, a granulocyte colony stimulating factor (G-CSF), is indicated for the following: 1) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever; 2) to reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML); 3) to reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation; 4) for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; 5) for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia; and 6) to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1] The FDA has approved Neupogen biosimilars, Zarxio (filgrastim-sndz) and Nivestym (filgrastim-aafi), for use in the US. Depending on the indication, filgrastim is given by subcutaneous (SC) bolus injection, by short intravenous (IV) infusion (15 to 30 minutes), or by continuous SC or continuous IV infusion.[1] Data supports the use of filgrastim in many other conditions.

POLICY STATEMENT

This policy involves the use of filgrastim. **This policy does not apply to Medicare or Medicare Advantage members.** Prior authorization is recommended for medical benefit coverage of Filgrastim. Coverage is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics** for the diagnosis provided. The requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section. **Zarxio (filgrastim-sndz) is the preferred filgrastim product as of November 1, 2018. Patient must have a documented failure, contraindication, intolerance, or ineffective response to Zarxio for a non-preferred filgrastim product to be considered for approval.**

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Filgrastimas well as the monitoring required for adverse events and long-term efficacy, initial approval requires Filgrastim to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is required, a response to therapy is required for continuation of therapy.

*The site of care medical necessity criteria applies to initial therapy and reauthorizations under the medical benefit.

FDA-Approved Indications

1. **Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy.**

Criteria. *The patient must meet the following criteria (A, B. C and D):*

A) The Filgrastim is prescribed by, or in consultation with, an oncologist or hematologist; AND

B) The patient meets ONE of the following conditions (i, ii, iii, or iv):

- **i.** The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR
- **ii.** The patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia but the risk is less than 20% based on the chemotherapy regimen and the patient has one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., aged ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus [HIV] infection); OR
- **iii.** The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (e.g., Granix™ [tbo-filgrastim injection], Leukine® [sargramostim injection], Neulasta® [pegfilgrastim injection], Filgrastim) and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
- **iv.** The patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescribing physician (e.g., sepsis syndrome; age > 65 years; severe neutropenia [absolute neutrophil count {ANC} < 100 cells/mm^3]; neutropenia expected to be > 10 days in duration; invasive fungal infection; other clinically documented infections); AND

C) If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND

D) Site of care medical necessity is met.*

Filgrastim is indicated for this condition to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia and fever.[1-4] The National Comprehensive Cancer Network (NCCN) guidelines for myeloid growth factors (version 1.2017) recommend Filgrastim, along with other CSFs, for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[3] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with a CSF in other scenarios in those given myelosuppressive chemotherapy.

Dosing in Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy. *Dosing must meet the following:* The starting dose is 5 mcg per kg per day by SC or IV injection for up to 2 weeks. Doses may be increased in increments of 5 mcg per kg according to the duration and severity of the absolute neutrophil count (ANC) nadir after chemotherapy.

The recommended starting dose of Filgrastim is 5 mcg/kg/day given as a single daily injection by SC injection, by short IV infusion (15 to 30 minutes), or by continuous IV infusion. Dose increases in increments of 5 mcg/kg may be considered for each chemotherapy cycle and is according to the duration and severity of the ANC nadir. It is recommended to stop Filgrastim if the ANC increases beyond 10,000 cells/mm^3. Filgrastim is given at least 24 hours after cytotoxic chemotherapy, and should not be given within the 24-hour period before chemotherapy. A transient increase in the neutrophil count is usually seen 1 to 2 days after starting Filgrastim. To ensure a sustained therapeutic response, these agents are given daily for up to 2 weeks or until the ANC reaches 10,000 cells/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of therapy needed may depend on the myelosuppressive potential of the chemotherapy regimen that is used. According to the NCCN guidelines for myeloid growth factors, the SC route is preferred. Filgrastim is started the next day to up to 3 to 4 days after completion of chemotherapy and treatment continues through post-nadir recovery. Because the duration of neutropenia often increases with each cycle of chemotherapy, longer periods of therapy with a CSF may be required for later chemotherapy cycles than for early cycles.

Initial Approval/Extended Approval.

A) *Initial Approval*. Initial approval is for up to 6 months.

B) *Extended Approval*. Extended approval is for up to 6-month intervals if the patient continues to receive myelosuppressive chemotherapy.

Duration of Therapy in Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy. Therapy may be continued as long as the patient is receiving myelosuppressive chemotherapy.

Labs/Diagnostics. None required.

2. <u>Adults with Acute Myeloid Leukemia (AML) Receiving Chemotherapy</u>.

Criteria. *<u>The patient must meet the following criteria (A, B, and C)</u>:*

A. Filgrastim is prescribed by, or in consultation with, an oncologist or hematologist; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Filgrastim is indicated to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

Dosing in AML. *<u>Dosing must meet the following</u>:* The starting dose is 5 mcg per kg per day by SC or IV injection for up to 2 weeks and starting 24 hours after the last dose of chemotherapy until neutrophil recovery that is usually for a maximum of 35 days. Doses may be increased in increments of 5 mcg per kg according to the duration and severity of the absolute neutrophil count (ANC) nadir after chemotherapy.

The recommended starting dose of Filgrastim is 5 mcg/kg/day given as a single daily injection by SC injection, by short IV infusion (15 to 30 minutes), or by continuous IV infusion. Dose increases in increments of 5 mcg/kg may be considered for each chemotherapy cycle and is according to the duration and severity of the ANC nadir. It is recommended to stop Filgrastim if the ANC increases beyond 10,000 cells/mm^3. Filgrastim is given at least 24 hours after cytotoxic chemotherapy, and should not be given within the 24-hour period before chemotherapy. A transient increase in the neutrophil count is usually seen 1 to 2 days after starting Filgrastim. To ensure a sustained therapeutic response, these agents are given daily for up to 2 weeks or until the ANC reaches 10,000 cells/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of therapy needed may depend on the myelosuppressive potential of the chemotherapy regimen that is used. Filgrastim is given following induction chemotherapy and for consolidation chemotherapy (i.e., post-remission chemotherapy).

Initial Approval/Extended Approval.
A) *<u>Initial Approval</u>*. Initial approval is for up to 6 months.
B) *<u>Extended Approval</u>*. Extended approval is at 6-month intervals.

Duration of Therapy in AML. Therapy may be continued as long as the patient is receiving chemotherapy. Some patients will receive an autologous or allogeneic hematopoietic stem cell transplantation and may require Filgrastim after peripheral blood progenitor cell (PBPC) collection. See Criteria 4 below.

Labs/Diagnostics. None required.

3. Patients with Cancer Receiving Bone Marrow Transplant (BMT).

Criteria. *The patient must meet the following criteria (A, B, and C):*

A. Filgrastim is prescribed by, or in consultation with, a hematologist, an oncologist, or a physician that specializes in transplantation; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Filgrastim is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by BMT. This criterion is recommended based on the professional opinion of specialized and other physicians.

Dosing in BMT. *Dosing must meet the following:* 10 mcg per kg per day given as an IV infusion no longer than 24 hours. During the period of neutrophil recovery, the dose should be titrated according to the absolute neutrophil count (ANC). Doses up to 30 mcg per kg per day have been used. Alternative dosing will be assessed individually on a case-by-case basis.

The recommended dose of Filgrastim after BMT is 10 mcg/kg/day given as an IV infusion for no longer than 24 hours.[1-2] The first dose is given at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. During the period of neutrophil recovery, the daily dosage of Filgrastim is titrated according to the neutrophil response. Recommendations for dosage adjustments during neutrophil recovery are as follows: 1) when the ANC is > 1,000 cells/mm^3 for 3 consecutive days, reduce the dose to 5 mcg/kg/day; 2) then, if the ANC remains > 1,000 cells/mm^3 for 3 or more consecutive days, discontinue Filgrastim; and 3) then, if ANC decreases to < 1,000 cells/mm^3 resume at 5 mcg/kg/day. If the ANC decreases to < 1,000 cells/mm^3, at any time during the 5 mcg/kg/day administration, increase the dose to 10 mcg/kg/day, and then follow the previous steps. In the pivotal trials establishing efficacy of Filgrastim in patients with cancer receiving BMT, the dose of these agents was 10 mcg/kg/day or 30 mcg/kg/day.

Initial Approval/Extended Approval.
A) *Initial Approval*. Approve for 1 month.
B) *Extended Approval*. Not applicable.

Duration of Therapy in BMT. Use is short-term after BMT (up to one month). Alternative durations will be assessed individually on a case-by-case basis.

Labs/Diagnostics. None required.

4. Patients (Adults and Children) Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy.

Criteria. *Patient must meet the following criteria (A, B, and C):*

A. Filgrastim is prescribed by, or in consultation with, an oncologist, a hematologist, or a physician that specializes in transplantation; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Filgrastim is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to a more rapid engraftment, which may result in a decreased need for supportive care. The scenarios where Filgrastim are utilized includes patients with cancer or healthy donors undergoing mobilization of PBPC, as well as patients with cancer post autologous PBPC transplantation. This criterion is recommended based on the professional opinion of specialized and other physicians.

Dosing in Patients (Adults and Children) Undergoing PBPC Collection and Therapy. *Dosing must meet ONE of the following (A, B, OR C):*

A) Patients with Cancer or Healthy Donors Undergoing Mobilization for PBPC: 10 mcg per kg per day SC, either as a bolus or continuous infusion for 5 to 7 days. Some patients may require up to 32 mcg per kg per day SC. Dosing can be once daily or twice daily. Alternate dosing will be assessed individually on a case-by-case basis.

The recommended dosage of Filgrastim for the mobilization of autologous PBPC is 10 mcg/kg/day as a SC injection. Filgrastimis given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis. The optimal duration of Filgrastim administration and leukapheresis schedule have not been established, but Filgrastim is usually administered for 6 to 7 days with leukapheresis on Days 5, 6, and 7 and was safe and effective in patients with cancer who were undergoing PBPC collection for autologous transplantation. Filgrastim is discontinued if the white blood cell count increases to > 100,000 cells/mm^3. Other sources indicate 5 days of Filgrastim 10 mcg per kg per day is adequate but some patients may require a longer duration of therapy (see duration of therapy section). Twice daily dosing may be utilized in certain circumstances.

B) Patients Undergoing Mobilization of PBPC Who Are Poor Mobilizers: 12.5 to 50 mcg per kg per day IV or SC. Dosing can be once daily or twice daily. Alternate dosing will be assessed individually on a case-by-case basis.

Poor mobilizers (e.g., patients who fail to mobilize an adequate number of stem cells on the first attempt; patients with Hodgkin's lymphoma, non-Hodgkin's lymphoma, and preleukemic syndromes; recent chemotherapy or radiation), may use Filgrastim or use other regimens that add Leukine to Filgrastim, add Mozobil® (plerixafor injection), or mobilization with chemotherapy plus Filgrastim.

C) Patients with Cancer Post Autologous PBPC Transplantation: 5 to 24 mcg per kg per day after reinfusion of the collected cells until a sustainable ANC is attained. Dosing can be once daily or twice daily. Alternative dosing will be assessed individually on a case-by-case basis.

In clinical trials of Filgrastim for mobilization of hematopoietic progenitor cells, Filgrastim was given to patients at doses of 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC $\geq$ 500 cells/mm^3 was reached. Another recommendation for supportive care in patients post autologous stem cell or cord blood transplant, is to give Filgrastim 5 mcg/kg/day beginning $\geq$ 5 days post transplant until recovery of ANC (e.g., > 1,500 cells/mm^3 for 2 consecutive days).

Initial Approval/Extended Approval.
Patients with Cancer or Healthy Donors Undergoing Mobilization of PBPC.

A) *Initial Approval*. For unrelated healthy donors, 5 days of therapy with Filgrastim 10 mcg per kg per day are used. For patients with cancer, 5 to 7 days of Filgrastim 10 mcg per kg per day are usually given once daily; twice daily dosing may be used. Alternative regimens will be assessed individually on a case-by-case basis and may be extended for some patients (e.g., patients who are poor mobilizers).

B) *Extended Approval*. Not applicable.

Patients with Cancer Post Autologous PBPC Transplantation.

A) *Initial Approval*. 14 days or until the absolute neutrophil count (ANC) is > 1,500 cells/mm^3 for 3 consecutive days. Usually the duration of therapy is 9 to 11 days but has ranged from 7 to 63 days. Alternative regimens will be assessed individually on a case-by-case basis.

B) *Extended Approval*. Not applicable.

Duration of Therapy in PBPC.

Patients with Cancer or Healthy Donors Undergoing Mobilization of PBPC. 5 days of Filgrastim .Alternative durations will be assessed individually on a case-by-case basis and may be extended for some patients (e.g., patients who are poor mobilizers).

The National Marrow Donor Program protocol gives Filgrastim for 4 consecutive days (in patients weighing < 35 kg) or 5 consecutive days in unrelated donors (allogeneic transplantation). In some instances, patients may require a longer duration of therapy (e.g., patients with cancer heavily pretreated with chemotherapy, healthy patients in which a higher number of cells are needed due to the type of transplantation).

Patients with Cancer Post Autologous PBPC Transplantation. 14 days of Filgrastim.Approve for another 14 days if ANC is not at a sustainable level. Most patients have a response after 28 days of Filgrastim. Alternative durations will be assessed individually on a case-by-case basis.

Labs/Diagnostics. None required.

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5. Patients (Adults and Children) with Severe Chronic Neutropenia (e.g., Congenital Neutropenia, Cyclic Neutropenia, Idiopathic Neutropenia).

Criteria. *The patient must meet the following criteria (A, B, and C)*:

A. Filgrastim is prescribed by, or in consultation with, a hematologist; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Filgrastim is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. The criteria is recommended based on the professional opinion of specialized and other physicians.

Dosing in Severe Chronic Neutropenia. *Dosing must meet the following*: The starting dose in congenital neutropenia is 6 mcg per kg twice daily (BID) by SC injection. For idiopathic or cyclic neutropenia, the starting dose is 5 mcg per kg SC once daily. The dose is adjusted based on the clinical response and the ANC. Alternative dosing will be assessed individually on a case-by-case basis.

The recommended starting dose in congenital neutropenia is 6 mcg/kg BID by SC injection. The recommended starting dose in patients with idiopathic or cyclic neutropenia is 5 mcg/kg as a single daily SC injection. In patients with severe chronic neutropenia, chronic daily administration is required. The dosage is individualized based on the patient's clinical course and the ANC. In the severe chronic neutropenia post-marketing surveillance study, the median daily doses of Filgrastim were: 6 mcg/kg (congenital neutropenia); 2.1 mcg/kg (cyclic neutropenia); and 1.2 mcg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of Filgrastim ≥ 100 mcg/kg/day. Many different doses have been used long-term. ANC should not be used as the sole indication of efficacy. Some data show that patients with idiopathic and cyclic neutropenia generally respond to low-dose daily, alternative day, or thrice-per-week Filgrastim (1 to 3 mcg per kg per day SC). Patients with congenital neutropenia generally require higher doses of 3 to 10 mcg per kg per day.

Initial Approval/Extended Approval.
A) *Initial Approval*. Initial approval is for up to 6 months.
B) *Extended Approval*. Extended approval is for up to 6 months.

Duration of Therapy in Patients with Severe Chronic Neutropenia. Therapy is chronic.

Labs/Diagnostics. None required.

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6. Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).

Criteria. *The patient must meet the following criteria (A, B, and C):*

A. Filgrastim is prescribed by, or in consultation with, a physician with expertise in treating acute radiation syndrome; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Filgrastim is indicated to increase survival in patients acutely exposed to myelosuppressive dose of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1] The recommended dose of Filgrastim is 10 mcg/kg as a single daily SC injection for patients exposed to myelosuppressive radiation doses. Administer Filgrastim as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray. Continue Filgrastim therapy until the absolute neutrophil count remains greater than 1,000/mm^3 for 3 consecutive days. It is notable that due to ethical and feasibility reasons, studies investigating the efficacy of Filgrastim could not be done in humans with acute radiation syndrome. Approval of Filgrastim for this use was based on efficacy studies performed in in animals and data supporting the use of Filgrastim for other approved indications.[1] Other sources also cite filgrastim being used for this scenario.[9-10]

Dosing in Patients with Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome). *Dosing must meet the following:* 10 mcg per kg per day SC.[1]

The recommended dose of Filgrastim is 10 mcg/kg as a single daily SC injection for patients exposed to myelosuppressive doses of radiation. Filgrastim is given as soon as possible after suspected or confirmed exposure to radiation doses of greater than 2 grays. The patient's absorbed radiation dose (i.e., level of radiation exposure) is estimated based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics. A baseline complete blood count (CBC) is obtained, and then serial CBCs are done approximately every third day until the ANC remains > 1,000 cells/mm^3 for three consecutive CBCs. Administration of Filgrastim is not delayed if a CBC is not readily available. Administration of Filgrastim is continued until the ANC remains > 1,000 cells/mm^3 for three consecutive CBCs or exceeds 10,000 cells/mm^3 after a radiation-induced nadir.

Initial Approval/Extended Approval.
A) *Initial Approval*. Initial approval is for 1 month.
B) *Extended Approval*. Approve at 1-month intervals.

Duration of Therapy in Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome). Usually only one course is needed until the ANC is adequate.

Labs/Diagnostics required. None required.

Other Uses with Supportive Evidence

7. Neutropenia Associated with Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS) in Adults.

Criteria. *Patient must meet the following criteria (A, B, and C)*:

A. Filgrastim is prescribed by, or in consultation with, a physician that specializes in infectious diseases, a hematologist, or a physician that specializes in the management of HIV/AIDS; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Neutropenia occurs in patients with HIV and may be caused by medications or due to the disease process. Studies have assessed use of Filgrastim for the treatment of neutropenia in this patient population.[12-15] In one open-label, non-comparative, multicenter study involving 200 HIV-positive patients Filgrastim reversed neutropenia in 98% of patients with a median reversal time of 2 days.[13] In another multicenter, randomized, controlled, open-label trial, use of daily Filgrastim or intermittent Filgrastim reduced the incidence of severe neutropenia or death compared with control patients who had advanced HIV infection.[12] Additionally, those receiving Filgrastim developed fewer bacterial infections.

Dosing for Neutropenia in Adults with HIV or AIDS. *Dosing must meet the following:* Filgrastim 5 to 10 mcg per kg SC once per day.

Initial Approval/Extended Approval.
A) *Initial Approval*. Initial approval is for 4 months.
B) *Extended Approval*. Extended approval is at 4-month intervals.

Duration of Therapy for Neutropenia in Adults with HIV or AIDS. Use may be long-term due to the nature of the disease and/or the need to continue medication therapy.

Labs/Diagnostics. None required.

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8. Treatment of Myelodysplastic Syndrome (MDS) in Adults.

Criteria. *Patient must meet the following criteria (A, B, and C)*:

A. Filgrastim is prescribed by, or in consultation with, an oncologist or hematologist; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

The NCCN guidelines on MDS (version 2.2017) recommend Filgrastim for use in certain patients with MDS (e.g., neutropenic patients with recurrent or resistant infections, combination use with Epogen®/Procrit® [epoetin alfa injection] or Aranesp® [darbepoetin alfa injection]). In one trial, 39% (n = 48/123 assessable patients) of patients with MDS treated with erythropoietin plus G-CSF achieved an erythroid response. Also, 29% (n = 25/85) of transfusion-dependent patients became transfusion independent. Other data are available.

Dosing in MDS. *Dosing must meet the following:* The dose range of Filgrastim is 1 to 2 mcg per kg given 1 to 2 times per week SC or 5 mcg per kg once daily SC or IV.

Initial Approval/Extended Approval.
A) *Initial Approval*. Initial approval is for 3 months.
B) *Extended Approval*. Approve at 3-month intervals.

Duration of Therapy in MDS. Therapy is usually intermittent.

Labs/Diagnostics. None required.

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9. Aplastic Anemia (Adults and Children).

Criteria. Patient must meet the following criteria (A, B, and C):
A. Filgrastim is prescribed by, or in consultation with, a hematologist and; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Filgrastim has been utilized in the treatment of aplastic anemia, usually in combination with immunosuppressive therapy or with erythropoietin-stimulating products. In one multicenter, randomized, controlled study, patients with anemia associated with aplastic anemia (n = 131) were treated with G-CSF alone or with Epogen/Procrit. The response rates at 12 weeks in 110 evaluable patients were between 12.9% and 36.8%. Guidelines for aplastic anemia published by the British Committee for Standards in Haematology in 2009 state that a short course of G-CSF may be considered for severe systemic infections that are not responding to IV antibiotics and anti-fungal medications, but should be discontinued after 1 week if no increase in neutrophil count is noted.

Dosing in Aplastic Anemia. *Dosing must meet the following:* Filgrastim 5 mcg per kg per day SC once daily or 1 to 3 times per week SC.

Initial Approval/Extended Approval.
A) *Initial Approval*. Approve for 1 month.
B) *Extended Approval*. Approval is at 1-month intervals.

Duration of Therapy in Patients with Aplastic Anemia. Therapy is usually intermittent.

Labs/Diagnostics. None required.

10. Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia.

Criteria. Patient must meet the following criteria (A, B, and C):
A. Filgrastim is prescribed by, or in consultation with, a hematologist and; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.

Dosing in Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia. *Dosing must meet the following*: The dose range is 5 to 10 mcg per kg per day SC or 300 mcg per day SC once daily.

Initial Approval/Extended Approval.
A) *Initial Approval*. Approve for 1 month.
B) *Extended Approval*. Approve at 1-month intervals.

Duration of Therapy in Patients with Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia. Therapy is usually short-term (up to 1 month).

Labs/Diagnostics. None required.

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11. Acute Lymphocytic Leukemia (ALL).

Criteria. Patient must meet the following criteria (A, B, and C):
A. Filgrastim is prescribed by, or in consultation with, a hematologist or an oncologist and; AND
B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
C. Site of care medical necessity is met.*

Data notes some benefits in patients with ALL in selected scenarios. This criterion is recommended based on the professional opinion of specialized and other physicians.

Dosing in ALL: *Dosing must meet the following:* Filgrastim dose is in the range of 5 to 10 mcg per kg per day SC.

Initial Approval/Extended Approval.
A) *Initial Approval*. Approval is for up to 1 month.
B) *Extended Approval*. Not applicable.

Duration of therapy in patients with ALL. Use is short-term.

Labs/Diagnostics. None required.

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12. Radiation-Induced Neutropenia.

Criteria. *Patient must meet the following criteria (A, B, C, and D).*
A) Filgrastim is prescribed by, or in consultation with, an oncologist, radiologist, or radiation oncologist; AND
B) The patient is not concurrently receiving chemotherapy; AND
C) If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND
D) Site of care medical necessity is met.*

ASCO guidelines, updated in 2015, state that CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. However, the Filgrastim prescribing information notes that the safety and efficacy of Filgrastim have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of Filgrastim with chemotherapy and radiation therapy should be avoided. The ASCO guidelines state that CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly

involving the mediastinum. The NCCN guidelines for myeloid growth factors (version 1.2017) state the prophylactic use of CSFs in patients given concurrent chemotherapy and radiation is not recommended. In one trial that administered radiotherapy with simultaneous chemotherapy, an unexpected reduced local control was reported.

Dosing in Radiation-Induced Neutropenia. *Dosing must meet the following*: The dose of Filgrastim is 5 mcg per kg per day SC or 300 mcg SC daily.

Initial Approval/Extended Approval.
A) *Initial Approval*. Approve for 6 months.
B) *Extended Approval*. Approve at 6-month intervals.

Duration of Therapy in Radiation-Induced Neutropenia. Therapy may continue as long as the patient is receiving radiation therapy.

Labs/Diagnostics. None required

Waste Management for All Indications.
Single-use vials and syringes contain 300 and 480 mcg of Filgrastim. Dose is sometimes based on a mcg per kg body weight basis with dose adjustment as needed. Use the most efficient formulation that delivers the needed dose.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Filgrastim has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances *not* listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

2. **Concomitant use of Colony Stimulating Factors**: Colony Stimulating Factors are not recommended as combination therapy.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drugs provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

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FOR MEDICAL BENEFIT COVERAGE REQUESTS:

*MMO Site of Care Medical Necessity Criteria:

Medications in this policy will be administered in a place of service that identifies the location to be a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met†:

1. Age less than 21 years; or
2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
3. History of a severe adverse event from previous administration of the prescribed medication; or

4. Requested medication is being administered as follows:
    - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
    - administered with dialysis; or
5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
6. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

No initial doses are allowed in a hospital based outpatient facility without other above criteria being met.

[†]This criterion does not apply to Medicare or Medicare Advantage members.

Prior approval is required for HCPCS Codes J1442, Q5101, Q5110

HCPCS Code(s):	
J1442	Injection, filgrastim (g-csf), excludes biosimilars, 1 microgram
Q5101	Injection, filgrastim-sndz, biosimilar, (zarxio), 1 microgram
Q5110	Injection, filgrastim-aafi, biosimilar, 1 microgram (Nivestym) Effective 10/01/2018