Drug and Biologic Coverage Policy

Effective Date 2/1/2024
Next Review Date… 2/1/2025
Coverage Policy Number IP0528

Filgrastim

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Related Coverage Resources

Pegfilgrastim - (IP0070)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for formulary exceptions for the following filgrastim products:

- **Granix®** (tbo-filgrastim subcutaneous injection)
- **Neupogen®** (filgrastim intravenous or subcutaneous injection)
- **Releuko®** (filgrastim-ayow intravenous or subcutaneous injection)

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Coverage criteria are listed for products **in the below table**:

Non-Covered/Non-Preferred Product	Criteria

Granix (tbo-filgrastim)	**Granix is considered medically necessary when ANY of the following is met:** • Documented failure, intolerance, or inability to use (for example, dose less than 180 mcg) filgrastim-aafi (**Nivestym**) AND filgrastim-sndz (**Zarxio**) • Documentation of continuation of therapy to complete current cycle of myelosuppressive chemotherapy • Use in hematopoietic cell transplant
Neupogen (filgrastim)	**Neupogen is considered medically necessary when ANY of the following is met:** • Documented failure, intolerance, or inability to use (for example, dose less than 180 mcg) filgrastim-aafi (**Nivestym**) AND filgrastim-sndz (**Zarxio**) • Documentation of continuation of therapy to complete current cycle of myelosuppressive chemotherapy • Use in hematopoietic cell transplant
Releuko (filgrastim-ayow)	**Releuko is considered medically necessary when ANY of the following is met:** • Documented failure, intolerance, or inability to use (for example, dose less than 180 mcg) filgrastim-aafi (**Nivestym**) AND filgrastim-sndz (**Zarxio**) • Documentation of continuation of therapy to complete current cycle of myelosuppressive chemotherapy • Use in hematopoietic cell transplant

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of filgrastim products (Granix, Neupogen, or Releuko) is considered medically necessary when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial and reauthorization is up to 1 month

Conditions Not Covered

Any other use is considered not medically necessary.

Coding

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1442	Injection, filgrastim (g-csf), excludes biosimilars, 1 microgram
J1447	Injection, tbo-filgrastim, 1 mcg
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5110	Injection, filgrastim-aafi, biosimilar, (Nivestym), 1 microgram
Q5125	Injection, filgrastim-ayow, biosimilar, (Releuko), 1 microgram

Background

OVERVIEW

Filgrastim, a leukocyte growth factor, is indicated for the following uses:[1-4]

- **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.
- **Mobilization of hematopoietic progenitor cells,** into the peripheral blood for collection by leukapheresis.
- **Reduce the time to neutrophil recovery and the duration of fever,** following induction or consolidation chemotherapy treatment of adults 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.
- **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.

Nivestym, Releuko, and Zarxio are biosimilars to Neupogen.[2-4] Releuko indication labeling does not include mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.[4] Neupogen is additionally indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1] Granix, a leukocyte growth factor, is indicated to reduce the duration of severe neutropenia in adults and pediatric patients ≥ 1 month of age with non-myeloid malignancies receiving myelosuppressive anti-cancer medications associated with a clinically significant incidence of febrile neutropenia.

Guidelines

The National Comprehensive Cancer Network (NCCN) addresses the use of filgrastim products in several guidelines.

- **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 2.2023 **–** July 28, 2023) recommend granulocyte colony stimulating factors (CSFs) as supportive care for myelosuppressive blocks of therapy or as directed by treatment protocol.[5]
- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend filgrastim for hematopoietic cell mobilization for allogeneic or autologous donors as a single agent or in combination with other treatments.[6]
- **Hematopoietic Growth Factors:** Guidelines (version 2.2023 – March 6, 2023) 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.[7] 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 CSFs in other scenarios in those given myelosuppressive chemotherapy. Filgrastim products are also recommended for mobilization and following hematopoietic cell transplant.
- **Management of Immunotherapy-Related Toxicities:** Guidelines (version 2.2023 – May 9, 2023) recommend granulocyte CSFs as supportive care for neutropenic patients with Grade 1 cytokine release syndrome resulting from chimeric antigen receptor T-cell therapy.[8]

- **Myelodysplastic Syndromes (MDS):** Guidelines (version 1.2023 – September 12, 2022) consider filgrastim for use in certain patients (e.g., neutropenic patients with recurrent or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia).[9]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommend CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[10] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

Other Uses with Supportive Evidence
Neutropenia occurs in patients with human immunodeficiency virus (HIV) and may be caused by medications or due to the disease process. Studies have demonstrated positive outcomes with the use of filgrastim for the treatment of neutropenia in this patient population.[11-14]

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.[15-21]

FDA Recommended Dosing

Product	FDA Recommended Dosing
Granix (tbo-filgrastim)	The recommended dose of Granix is 5 mcg/kg per day administered as a subcutaneous injection. Administer the first dose of Granix no earlier than 24 hours following myelosuppressive chemotherapy. Do not administer Granix within 24 hours prior to chemotherapy. Daily dosing with Granix should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Monitor complete blood count (CBC) prior to chemotherapy and twice per week until recovery.
Neupogen (filgrastim)	**Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML** The recommended starting dosage of Neupogen is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting Neupogen therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping Neupogen if the ANC increases beyond 10,000/mm^3. Administer Neupogen at least 24 hours after cytotoxic chemotherapy. Do not administer Neupogen within the 24-hour period prior to chemotherapy. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of Neupogen therapy. Therefore, to ensure a sustained therapeutic response, administer Neupogen daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of Neupogen therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. **Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation** The recommended dosage of Neupogen following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. Administer the first dose of Neupogen at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. Monitor CBCs and platelet counts frequently following marrow transplantation.

During the period of neutrophil recovery, titrate the daily dosage of Neupogen against the neutrophil response (see Table 1).

Table 1: Recommended Dosage Adjustments During Neutrophil Recovery in Patients with Cancer Following BMT

Absolute Neutrophil Count	Neupogen Dosage Adjustment
When ANC greater than 1000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day[a]
Then, if ANC remains greater than 1000/mm^3 for 3 more consecutive days	Discontinue Neupogen
Then, if ANC decreases to less than 1000/mm^3	Resume at 5 mcg/kg/day

[a] If ANC decreases to less than 1000/mm^3 at any time during the 5 mcg/kg/day administration, increase Neupogen to 10 mcg/kg/day, and then follow the above steps.

Dosage in Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The recommended dosage of Neupogen for the mobilization of autologous peripheral blood progenitor cells (PBPC) is 10 mcg/kg/day given by subcutaneous injection. Administer Neupogen for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of Neupogen administration and leukapheresis schedule have not been established, administration of Neupogen for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective. Monitor neutrophil counts after 4 days of Neupogen, and discontinue Neupogen if the white blood cell (WBC) count rises to greater than 100,000/mm^3.

Dosage in Patients with Severe Chronic Neutropenia

Prior to starting Neupogen in patients with suspected chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. The use of Neupogen prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

The recommended starting dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection and the recommended starting dosage in patients with Idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection.

Dosage Adjustments in Patients with Severe Chronic Neutropenia

Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC. In the SCN post-marketing surveillance study, the reported median daily doses of Neupogen 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 Neupogen greater than or equal to 100 mcg/kg/day.

Monitor CBCs for Dosage Adjustments

During the initial 4 weeks of Neupogen therapy and during the 2 weeks following any dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if the patient is clinically stable, less frequent routine monitoring is recommended.

Dosage in Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

<table>
<tr><td></td><td>The recommended dose of Neupogen is 10 mcg/kg as a single daily subcutaneous injection for patients exposed to myelosuppressive doses of radiation. Administer Neupogen as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).

Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

Obtain a baseline CBC and then serial CBCs approximately every third day until the ANC remains greater than 1,000/mm3 for 3 consecutive CBCs. Do not delay administration of Neupogen if a CBC is not readily available.

Continue administration of Neupogen until the ANC remains greater than 1,000/mm^3 for 3 consecutive CBCs or exceeds 10,000/mm^3 after a radiation-induced nadir.</td></tr>
<tr><td>Nivestym
(filgrastim-aafi)</td><td>Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML
The recommended starting dosage of Nivestym is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting Nivestym therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping Nivestym if the ANC increases beyond 10,000/mm^3.

Administer Nivestym at least 24 hours after cytotoxic chemotherapy. Do not administer Nivestym within the 24-hour period prior to chemotherapy. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of Nivestym therapy. Therefore, to ensure a sustained therapeutic response, administer Nivestym daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of Nivestym therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation
The recommended dosage of Nivestym following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. Administer the first dose of Nivestym at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. Monitor CBCs and platelet counts frequently following marrow transplantation.

During the period of neutrophil recovery, titrate the daily dosage of Nivestym against the neutrophil response (see Table 1).
Table 1: Recommended Dosage Adjustments During Neutrophil Recovery in Patients with Cancer Following BMT
<table>
<tr><th>Absolute Neutrophil Count</th><th>Nivestym Dosage Adjustment</th></tr>
<tr><td>When ANC greater than 1000/mm^3 for 3 consecutive days</td><td>Reduce to 5 mcg/kg/day[a]</td></tr>
<tr><td>Then, if ANC remains greater than 1000/mm^3 for 3 more consecutive days</td><td>Discontinue Nivestym</td></tr>
<tr><td>Then, if ANC decreases to less than 1000/mm^3</td><td>Resume at 5 mcg/kg/day</td></tr>
</table>
a If ANC decreases to less than 1000/mm^3 at any time during the 5 mcg/kg/day administration, increase Nivestym to 10 mcg/kg/day, and then follow the above steps.</td></tr>
</table>

	Dosage in Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy The recommended dosage of Nivestym for the mobilization of autologous peripheral blood progenitor cells (PBPC) is 10 mcg/kg/day given by subcutaneous injection. Administer Nivestym for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of Nivestym administration and leukapheresis schedule have not been established, administration of filgrastim for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective. Monitor neutrophil counts after 4 days of Nivestym, and discontinue Nivestym if the white blood cell (WBC) count rises to greater than 100,000/mm^3. **Dosage in Patients with Severe Chronic Neutropenia** Prior to starting Nivestym in patients with suspected chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. The use of Nivestym prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia. The recommended starting dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection and the recommended starting dosage in patients with Idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection. <u>Dosage Adjustments in Patients with Severe Chronic Neutropenia</u> Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC. In the SCN post-marketing surveillance study, the reported 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 greater than or equal to 100 mcg/kg/day. <u>Monitor CBCs for Dosage Adjustments</u> During the initial 4 weeks of Nivestym therapy and during the 2 weeks following any dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if the patient is clinically stable, less frequent routine monitoring is recommended.
Releuko (filgrastim-ayow)	**Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML** The recommended starting dosage of Releuko is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting Releuko therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping Releuko if the ANC increases beyond 10,000/mm3 [*see Warnings and Precautions (5.10*)]. Administer Releuko at least 24 hours after cytotoxic chemotherapy. Do not administer Releuko within the 24 hour period prior to chemotherapy [*see Warnings and Precautions (5.13*)]. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of Releuko therapy. Therefore, to ensure a sustained therapeutic response, administer Releuko daily for up to 2 weeks or until the ANC has reached 10,000/mm3 following the expected chemotherapy-induced neutrophil nadir. The duration of Releuko therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation
The recommended dosage of Releuko following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. Administer the first dose of Releuko at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. Monitor CBCs and platelet counts frequently following marrow transplantation.

During the period of neutrophil recovery, titrate the daily dosage of Releuko against the neutrophil response (*see Table 1*).

Table 1: Recommended Dosage Adjustments During Neutrophil Recovery in Patients with Cancer Following BMT

Absolute Neutrophil Count	Nivestym Dosage Adjustment
When ANC greater than 1000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day[a]
Then, if ANC remains greater than 1000/mm^3 for 3 more consecutive days	Discontinue Releuko
Then, if ANC decreases to less than 1000/mm^3	Resume at 5 mcg/kg/day

[a] If ANC decreases to less than 1000/mm^3 at any time during the 5 mcg/kg/day administration, increase Releuko to 10 mcg/kg/day, and then follow the above steps.

Dosage in Patients with Severe Chronic Neutropenia
Prior to starting Releuko in patients with suspected chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. The use of Releuko prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

The recommended starting dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection and the recommended starting dosage in patients with Idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection.

Dosage Adjustments in Patients with Severe Chronic Neutropenia
Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC. In the SCN postmarketing surveillance study, the reported 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 greater than or equal to 100 mcg/kg/day.

Monitor CBCs for Dosage Adjustments
During the initial 4 weeks of Releuko therapy and during the 2 weeks following any dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if the patient is clinically stable, less frequent routine monitoring is recommended.

Under *Important Administration Instructions*: Releuko prefilled syringe with BD UltraSafe Passive™ Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to

<table>
<tr><td></td><td>accurately measure doses of Releuko less than 0.3 mL (180 mcg) for direct administration to patients. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors.</td></tr>
<tr><td>Zarxio
(filgrastim-sndz)</td><td>Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML
The recommended starting dosage of Zarxio is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting Zarxio therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping Zarxio if the ANC increases beyond 10,000/mm^3.

Administer Zarxio at least 24 hours after cytotoxic chemotherapy. Do not administer Zarxio within the 24-hour period prior to chemotherapy. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of Zarxio therapy. Therefore, to ensure a sustained therapeutic response, administer Zarxio daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of Zarxio therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation
The recommended dosage of Zarxio following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. Administer the first dose of Zarxio at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. Monitor CBCs and platelet counts frequently following marrow transplantation.

During the period of neutrophil recovery, titrate the daily dosage of Zarxio against the neutrophil response (see Table 1).
Table 1: Recommended Dosage Adjustments During Neutrophil Recovery in Patients with Cancer Following BMT
<table>
<tr><th>Absolute Neutrophil Count</th><th>Zarxio Dosage Adjustment</th></tr>
<tr><td>When ANC greater than 1000/mm^3 for 3 consecutive days</td><td>Reduce to 5 mcg/kg/day*</td></tr>
<tr><td>Then, if ANC remains greater than 1000/mm^3 for 3 more consecutive days</td><td>Discontinue Zarxio</td></tr>
<tr><td>Then, if ANC decreases to less than 1000/mm^3</td><td>Resume at 5 mcg/kg/day</td></tr>
</table>
* If ANC decreases to less than 1000/mm^3 at any time during the 5 mcg/kg/day administration, increase Zarxio to 10 mcg/kg/day, and then follow the above steps.

Dosage in Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
The recommended dosage of Zarxio for the mobilization of autologous peripheral blood progenitor cells (PBPC) is 10 mcg/kg/day given by subcutaneous injection. Administer Zarxio for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of Zarxio administration and leukapheresis schedule have not been established, administration of filgrastim for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective. Monitor neutrophil counts after 4 days of Zarxio, and discontinue Zarxio if the white blood cell (WBC) count rises to greater than 100,000/mm^3.

Dosage in Patients with Severe Chronic Neutropenia
Prior to starting Zarxio in patients with suspected chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet</td></tr>
</table>

	counts, and evaluating bone marrow morphology and karyotype. The use of Zarxio prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia. The recommended starting dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection and the recommended starting dosage in patients with Idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection. <u>Dosage Adjustments in Patients with Severe Chronic Neutropenia</u> Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC. In the SCN post-marketing surveillance study, the reported 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 greater than or equal to 100 mcg/kg/day. <u>Monitor CBCs for Dosage Adjustments</u> During the initial 4 weeks of Zarxio therapy and during the 2 weeks following any dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if the patient is clinically stable, less frequent routine monitoring is recommended. Under *Important Administration Instructions*: Zarxio prefilled syringe with BD UltraSafe Passive™ Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of Zarxio less than 0.3 mL (180 mcg) for direct administration to patients. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors.

Drug Availability

Product	Product Availability
Granix (tbo-filgrastim)	Supplied in single-dose vials containing 300 mcg/mL and 480 mcg/1.6 mL for injection and in single-dose prefilled syringes of 300 mcg/0.5 mL and 480 mcg/0.8 mL for injection.
Neupogen (filgrastim)	Supplied in single-dose vials containing 300 mcg/mL and 480 mcg/1.6 mL for injection and in single-dose prefilled syringes of 300 mcg/0.5 mL and 480 mcg/0.8 mL for injection.
Nivestym (filgrastim-aafi)	Supplied in single-dose vials containing 300 mcg/mL and 480 mcg/1.6 mL for injection and in single-dose prefilled syringes of 300 mcg/0.5 mL and 480 mcg/0.8 mL for injection.
Releuko (filgrastim-ayow)	Supplied in single-dose vials containing 300 mcg/mL and 480 mcg/1.6 mL for injection and in single-dose prefilled syringes of 300 mcg/0.5 mL and 480 mcg/0.8 mL for injection.
Zarxio (filgrastim-sndz)	Supplied as 300 mcg/0.5 mL and 480 mcg/0.8 mL for injection in single-dose prefilled syringes with BD UltraSafe Passive™ Needle Guard.

References

1. Neupogen® subcutaneous or intravenous injection [prescribing information]. Thousand Oaks, CA: Amgen; April 2023.
2. Zarxio™ subcutaneous or intravenous injection [prescribing information]. Princeton, NJ: Sandoz; March 2021.
3. Nivestym™ subcutaneous or intravenous injection [prescribing information]. Lake Forest, IL and New York, NY: Hospira and Pfizer; March 2023.
4. Releuko® subcutaneous or intravenous injection [prescribing information]. Bridgewater, NJ: Amneal; June 2023.
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