

Short-acting Agents: Zarxio® (filgrastim-sndz)

Nivestym® (filgrastim-aafi) Granix® (tbo-filgrastim) Neupogen® (filgrastim) Leukine® (sargramostim)

Long-acting Agents:

Ziextenzo® (pegfilgrastim-bmez)

Fulphila[™](pegfilgrastim-jmdb) Neulasta® (pegfilgrastim) Nyvepria® (pegfilgrastim-apgf) Udenyca® (pegfilgrastim-cbqv)

Preferred Short-acting Agents:

- Zarxio
- Requests for non-preferred short-acting agents require trial of Zarxio inaddition to meeting clinical criteria detailed below

Preferred Long-acting Agent:

- Ziextenzo
- Requests for non-preferred long-acting agents require trial of Ziextenzo in addition to meeting clinical criteria detailed below

General Authorization Criteria for ALL Agents and Indications:

- Prescribed by, or in consultation with hematologist or oncologist
- Medical records, labs, and weight or body surface area to support diagnosis and dosing
- Requested agent is dosed and administered within Food and Drug Administration labeled recommendations
 - Will not be used concomitantly with radiation and chemotherapy
 - o Will be administered at appropriate time after chemotherapy or radiation
- Member does not have any contraindications or hypersensitivity to requested agent
- Will not be used in combination with other myeloid growth factors

Additional Criteria Based on Indication:

Chemotherapy-Induced Febrile Neutropenia for members receiving chemotherapy for NON-myeloid cancer (solid tumor and lymphoid malignancies)

- **Primary prophylaxis** (Fulphila, Granix, Leukine, Neupogen, Neulasta, Nivestym, Nyvepria, Udenyca, Zarxio, Ziextenzo)
 - o Documentation to support member meets one of the following:
 - Chemotherapy regimen has greater than 20% risk of febrile neutropenia (refer to the Appendix)
 - Chemotherapy regimen has 10%-20% risk of febrile neutropenia (refer to the Appendix) AND member has one of the following risk factors for febrile neutropenia:
 - Age greater than 65 years
 - Prior chemotherapy or radiation therapy
 - Persistent neutropenia

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



- Bone marrow involvement by tumor
- Recent surgery, open wounds, or active infection
- Liver dysfunction (bilirubin great than 2.0 mg/dL)
- Renal dysfunction (creatinine clearance less than 50ml/min)
- Human immunodeficiency virus (HIV) infection
- **Secondary prophylaxis:** (Fulphila, Granix, Leukine, Neupogen, Neulasta, Nivestym, Nyvepria, Udenyca, Zarxio, Ziextenzo)
 - Documentation to support member previously experienced febrile neutropenia from same chemotherapy regimen (for which primary prophylaxis was not received), and reducing or delaying chemotherapy dose may compromise treatment outcome
 - Members with prior use of colony stimulating factor for same chemotherapy regimen who
 experience febrile neutropenia or neutropenic event should consider chemotherapy dose
 reduction or change in treatment regimen
- Treatment: (Granix, Leukine, Neupogen, Nivestym, Zarxio)
 - Documentation to support member has one of the following:
 - Members who received prophylaxis with short-acting colony stimulating factors should continue therapy
 - Members who did not receive prophylaxis AND have risk factors for infection-associated complication (for example: age greater than 65 years, absolute neutrophil count less than 100 neutrophils/microliter, neutropenia expected to be greater than 10 days, pneumonia, invasive fungal infection, hospitalization at time of fever, and prior episode of febrile neutropenia)
 - Members who received prophylaxis with long-acting colony stimulating factors do not require additional therapy with short-acting colony stimulating factors unless there is prolonged neutropenia
- Bone marrow/stem cell transplant: (Leukine, Neupogen, Nivestym, Zarxio)
 - Documentation to support member has one of the following:
 - Non-myeloid malignancies and undergoing myeloablative chemotherapy followed by autologous or allogeneic bone marrow transplant (BMT)
 - Used for mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis
 - Member had peripheral stem cell transplant (PSCT) and received myeloablative chemotherapy
- Severe chronic congenital, cyclic, or idiopathic neutropenia: (Neupogen, Nivestym, Zarxio)
 - Documentation to support member has experienced an infection requiring antibiotic treatment during previous 12 months and one of the following:
 - For chronic neutropenia: documented absolute neutrophil count less than 500 neutrophils/microliter on three occasions during a 6-month period

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



- For cyclic neutropenia: documented 5 consecutive days of absolute neutrophil count less than 500 neutrophils/microliter per cycle
- Neutropenia related to Humanimunodeficiency Virus (HIV): (Leukine, Neupogen, Nivestym, Zarxio)
 - o Documentation to support diagnosis of advanced Human Immunodeficiency Virus infection
 - In addition to Hematology or Oncology specialty, the following prescriber specialties are also accepted for this indication:
 - Infectious Disease Specialist
 - Human Immunodeficiency Virus (HIV) Specialist
- Acute Myeloid Leukemia (AML) Induction or Consolidation Therapy: (Leukine, Neupogen, Nivestym, Zarxio)
 - Documentation to support diagnosis and member completed either induction or consolidation chemotherapy
- **Hematopoietic Syndrome of Acute Radiation Syndrome:** (Granix, Fulphila, Leukine, Neulasta, Neupogen, Nivestym, Nyvepria, Udenyca, Zarxio, Ziextenzo)
 - Documentation to support member has been acutely exposed to myelosuppressive doses of radiation

Initial Approval:

- Chemotherapy-induced neutropenia (primary or secondary prophylaxis)
 - o Approve per cycle of chemotherapy:
 - Up to a 14-day supply for Granix, Leukine, Neupogen, Nivestym, and Zarxio
 - One 6 mg dose of long-acting colony stimulating factors no less than every 14 days
 - Include refills if number of cycles is provided
- Treatment of neutropenia (bone marrow transplant, chronic congenital, cyclic, idiopathic neutropenia, Human Immunodeficiency Virus)
 - o Approve 3 months
- Allotherindications
 - o Approve up to 6 months or less

Renewal Approval:

Chemotherapy-induced neutropenia (primary or secondary prophylaxis)

- Recent absolute neutrophil counts howing response to the rapy
- Approve per cycle of chemotherapy:
 - o Up to a 14-day supply for Granix, Leukine, Neupogen, Nivestym, and Zarxio
 - o One 6 mg dose of long-acting colony stimulating factors no less than every 14 days
 - o Include refills if number of cycles is provided, or up to 12 months

All other indications

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



- Recent absolute neutrophil count (ANC) showing response to the rapy
 - o Approve up to 6 months

Additional Information

Febrile neutropenia: a single temperature greater than or equal to 38.3 degrees Celsius orally or greater than 38 degrees Celsius over an hour, with an absolute neutrophil count of less than 500 neutrophils/microliter or an absolute neutrophil count of less than 1000 neutrophils/microliter with a predicted decline to less than or equal to 500 neutrophils/microliter over the next 48 hours

Neutropenia: absolute neutrophil count of less than 1500 neutrophils/microliter

Severe neutropenia: absolute neutrophil count of less than 500 neutrophils/microliter

Determining risk of febrile neutropenia: A member's risk for developing neutropenic fever may be assessed prior to use of colony stimulating factors. This may be achieved by evaluating degree of myelosuppression of member's chemotherapy regimen in addition to presence of other member-related risk factors. Both Infectious Diseases Society of America and National Comprehensive Cancer Network recommend that colony stimulating factors be considered when risk of febrile neutropenia is > 20%.

Dosing Table:

Medication	Dosing	Available Dosage forms
Neupogen Zarxio Nivestym	 Febrile Neutropenia or acutemyeloidleukemia:5 mcg/kg/day (Not given 24 hours before chemotherapy and 24 hours after) Bone marrow transplant: 10 mcg/kg/day (given 24 hrs. after bone marrow transplant and given for at least 24 hours) Peripheral Blood Progenitor Cell: 10 mcg/kg/day; at least 4 days before and up to 7 days Severe Chronic Neutropenia: Idiopathic:1.2 mcg/kg/day Cyclic: 2.1 mcg/kg/day Congenital: 6 mcg/kg/day divided 2 times 	vial
Neulasta Fulphila Udenyca Ziextenzo	 Febrile Neutropenia: 6mg subcutaneously once per chemotherapy cycle for adults; Not given 14 days before chemotherapy to 24 hours after Acute radiation exposure: 6mg subcutaneously once, followed by a second dose of 6 mg subcutaneously 1 week later, for a total of two doses for adults. 	 6 mg/0.6 mL, single-dose prefilled syringe 6 mg/0.6 mL, single-dose prefilled syringe copackaged with the On-body Injector (Neulasta Onprokit)

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



	 Pediatric members (both indications): 45 kg or greater: 6 mg subcutaneously. 31 kg to 44 kg: 4 mg subcutaneously. 21 kg to 30 kg: 2.5 mg subcutaneously. 10 kg to 20 kg: 1.5 mg subcutaneously. Less than 10 kg: 0.1 mg/kg subcutaneously. 	
Leukine	 Acute myeloid leukemia: 250 mcg/m²/day intravenous on day 11- or 4-days following completion of induction chemotherapy Mobilization of peripheral blood progenitor cells: 250 mcg/ m²/day administered intravenously over 24 hours or subcutaneous injection once daily. Myeloid reconstitution after autologous or allogeneic bone marrow transplant: 250 mcg/m²/day administered intravenously over a 2-hour period BMT failure or engraftment delayed: 250 mcg/m²/day for 14 days as a 2-hour intravenous infusion Patients acutely exposed to myelosuppressive doses of radiation, administer once daily as subcutaneous injection: Adults and pediatric patients weighing >40 kg: 7 mcg/kg once daily Pediatric patients 15 kg to 40 kg: 10mcg/kg once daily Pediatric patients less than 15 kg: 12mcg/kg once daily Post Peripheral Blood Progenitor Cell Transplantation: 250mcg/m²/day SQ once or IV over 24 hours 	 500 mcg/mL vial 250 mcg powder for injection
Granix	 Febrile Neutropenia 5mcg/kg/day subcutaneous injection Not given 24 hours before chemotherapy to 24 hours after 	300mcg/0.5mL,single-use prefilled syringe480mcg/0.8mL, single use prefilled syringe

References:

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



- Fulphila (pegfilgrastim-jmdb) [prescribing information]. Rockford, IL: Mylan Institutional LLC. Last revision March 19, 2021. Retrieved from https://www.dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3ea915d7-2feb-4e75-91f7-913c965b7d8a#ID 936ed1c9-1185-44dc-9970-f272144abe0d. Accessed November 10, 2021.
- Granix(tbo-filgrastim)[packageinsert]. North Wales, PA: Cephalon, Inc. Last revision November 2019. Retrieved from https://www.granixhcp.com/globalassets/granix-hcp/prescribing-information.pdf. Accessed November 10, 2021.
- 3. Hermans P, Rozenbaum W, Jou A, et al. Filgrastim to treat neutropenia and support myelosuppressive medication dosing in HIV infection. G-CSF 92105 Study Group. AIDS. 1996;10(14):1627-1633.
- Infectious Disease Society of America: Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Members with Cancer: 2010 Update by the Infectious Diseases Society of America. Available at: https://academic.oup.com/cid/article/52/4/e56/382256. Accessed August 28, 2019.
- 5. Larson, R.A. (2021). Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation In. DMF Savarese (Ed.), Retrieved from <a href="https://www.uptodate.com/contents/use-of-granulocyte-colony-stimulating-factors-in-adult-patients-with-chemotherapy-induced-neutropenia-and-conditions-other-than-acute-leukemia-myelodysplastic-syndrome-and-hematopoietic-cell-transplantation. Accessed November 10, 2021.
- 6. Leukine [package insert]. Bridgewater, NJ: Sanofi-Aventis. Last revision May 2018. Retrieved from https://www.leukine.com/wp-content/uploads/2020/06/Prescribing_Information.pdf. Accessed November 10, 2021.
- 7. Levine JD, Allan JD, Tessitore JH, Falcone N, Galasso F, Israel RJ, Groopman JE. Recombinant human granulocyte-macrophage colony-stimulating factor ameliorates zidovudine-induced neutropenia in members with acquired immunodeficiency syndrome (AIDS)/AIDS-related complex. Blood. 1991;78:3148–3154.
- 8. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factor V.4.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed November 10, 2021.
- 9. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infection. V.1.2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf Accessed November 10, 2021.
- 10. Neulasta [package insert]. Thousand Oaks, CA: Amgen; Last revision February 2021. Retrieved from https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/neulasta/neulasta_pi_hcp_english.pdf. Accessed November 10, 2021.
- 11. Neupogen[package insert]. Thousand Oaks, CA: Amgen, Inc. Lastrevision February 2021. Retrieved from https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/neupogen/neupogen pi hcp english.pdf. Accessed November 10, 2021.
- 12. Nivestym (filgrastim-aafi) [prescribing information]. Lake Forest, IL: Pfizer; Last revision October 2021. Retrieved from http://labeling.pfizer.com/ShowLabeling.aspx?id=10899. Accessed November 10, 2021.
- 13. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. *J Clin Oncol* 24:3187-3205. Available at: http://jco.ascopubs.org/cgi/reprint/24/19/3187. Accessed July 30, 2018
- 14. Smith TJ, Bohlke K, Armitage JO. Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Oncol Pract. 2015 Nov;11(6):511-513. https://ascopubs.org/doi/full/10.1200/JOP.2015.006742. Accessed November 10, 2021.
- 15. Udenyca (pegfilgrastim-cbqv) [prescribing information]. Redwood City, CA: Coherus Biosciences; Last revision May 2021. Retrieved from https://udenyca.com/wp-content/pdfs/udenyca-pi.pdf. Accessed November 10, 2021.
- 16. Zarxio (filgrastim-sndz) [package insert]. Princeton, NJ: Sandoz Inc. Last revision March 1 2021. Retrieved from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c0d1c22b-566b-4776-bdbf-00f96dad0cae. Accessed November 10, 2021.
- 17. Ziextenzo [package insert]. Princeton, NJ: Sandoz Inc; Last revision March 2021. Retrieved from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7dada041-6528-4acf-809c-62d271538c9a. Accessed November 10, 2021.

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



Appendix

Table 1: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of Greater Than 20%

Cancer Histology	Regimen
Acute Lymphoblastic Leukemia (ALL)	Select ALL regimens as directed by treatment protocol (see NCCN guidelines)
Bladder Cancer	Dose dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
	CBDCa/Pac (carboplatin, paclitaxel)
Bone Cancer	VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)
	VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)
	VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)
	Cisplatin/doxorubicin
	VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin
Breast Cancer	Docetaxel + trastuzumab
	Dose-dense AC (doxorubicin, cyclophosphamide) + paclitaxel (or dose dense paclitaxel)
	TAC (docetaxel, doxorubicin, cyclophosphamide)
	AT (doxorubicin, docetaxel)
	Doc (docetaxel)
	TC (docetaxel, cyclophosphamide)

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



	TCH (docetaxel, carboplatin, trastuzumab)
Colorectal Cancer	FOLFOXIRI (Fluorouracil, leucovorin, oxaliplatin, irinotecan)
Esophageal and Gastric Cancers	Docetaxel/cisplatin/fluorouracil
Head and Neck Squamous Cell Carcinoma	TPF (docetaxel, cisplatin, 5-fluorouracil)
Hodgkin Lymphoma	Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)
	Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)
Kidney Cancer	Doxorubicin/gemcitabine
Melanoma	Dacarbazine-based combination with IL-2, interferon alpha (dacarbazine, cisplatin, vinblastine, IL-2, interferon alpha)
Multiple myeloma	DT-PACE (dexamethasone/ thalidomide / cisplatin / doxorubicin / cyclophosphamide / etoposide) + bortezomib (VTD-PACE)
	DT-PACE (dexamethasone / thalidomide / cisplatin / doxorubicin / cyclophosphamide/etoposide)
Non-Hodgkin's Lymphoma	Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
	ICE (ifosfamide, carboplatin, etoposide)
	Dose-dense CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
	MINE (mesna, ifosfamide, novantrone, etoposide)
	DHAP (dexamethasone, cisplatin, cytarabine)

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



	ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine (Ara-C))
	HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)
	VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin)
Ovarian Cancer	Topotecan
	Docetaxel
Pancreatic Cancer	FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin)
Soft Tissue Sarcoma	MAID (mesna, doxorubicin, ifosfammide, dacarbazine)
	Doxorubicin
	Ifosfamide/doxorubicin
Small Cell Lung Cancer	Top (topotecan)
	CAV (cyclophosphamide, doxorubicin, vincristine)
Testicular cancer	VelP (vinblastine, ifosfamide, cisplatin)
	VIP (etoposide, ifosfamide, cisplatin)
	TIP (paclitaxel, ifosfamide, cisplatin)

Source: Smith et al, 2006; NCCN Hematopoietic Growth Factors, 2020

Table 2: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of 10% to 20%

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021



Cancer Histology	Regimen
Occult primary - adenocarcinoma	Gemcitabine/docetaxel
Breast Cancer	Docetaxel
	CMF classic (cyclophosphamide, methotrexate, fluorouracil)
	CA (doxorubicin, cyclophosphamide) (60 mg/m²) (hospitalized)
	AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)
	AC + sequential docetaxel + trastuzumab
	A (doxorubicin) (75 mg/m²)
	AC (doxorubicin, cyclophosphamide)
	CapDoc (capecitabine, docetaxel)
	Paclitaxel every 21 days
Cervical Cancer	Irinotecan
	Cisplatin/topotecan
	Paclitaxel/cisplatin
	Topotecan
Colorectal	FL (fluorouracil, leucovorin)
	CPT-11 (irinotecan) (350 mg/m² q 3 wk)
	FOLFOX (fluorouracil, leucovorin, oxaliplatin)

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021

Effective: 2/2022



Esophageal and Gastric Cancers	Irinotecan/cisplatin
	Epirubicin/cisplatin/5-fluorouracil
	Epirubicin/cisplatin/capecitabine
Non-Hodgkin's lymphomas	EPOCH-IT chemotherapy
	GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)
	GDP (gemcitabine, dexamethasone, cisplatin/carboplatin) + rituximab
	FMR (fludarabine, mitoxantrone, rituximab)
	CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) including regiments with pegylated liposomal doxorubicin
	CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) including regimens with pegylated liposomal doxorubicin
	CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
	Bendamustine
Non-Small Cell Lung Cancer	Cisplatin/paclitaxel
	Cisplatin/vinorelbine
	Cisplatin/docetaxel
	Cisplatin/etoposide
	Carboplatin/paclitaxel
	Docetaxel
Ovarian Cancer	Carboplatin/docetaxel

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021

Effective: 2/2022



Prostate Cancer	Cabazitaxel
Small Cell Lung Cancer	Etoposide/carboplatin
Testicular Cancer	BEP (bleomycin, etoposide, cisplatin)
	Etoposide/cisplatin
Uterine Sarcoma	Docetaxel

Source: Smith et al, 2006; NCCN Hematopoietic Growth Factors, 2020

Last Update: 02/2019, 08/2019, 4/1/2020, 11/2020, 9/2021