Pharmacy Prior Authorization
Colony Stimulating Factor (CSF)/Myeloid Growth Factor (MGF) – Clinical Guideline

Zarxio® (filgrastrim-sndz)
Granix® (tbo-filgrastim)
Fulphila™ (pegfilgrastim-jmdb)
Neulasta® (peg-filgrastim; G-CSF)
Leukine® (sargramostim; GM-CSF)
Nivestym™ (filgrastim-aafi)
Neupogen® (filgrastim; G-CSF)
Udenyca™ (pegfilgrastim-cbqv)
Neulasta Onpro® (peg-filgrastim; G-CSF)

Preferred Agent:

- Zarxio and Nivestym are the preferred short acting Granulocyte Colony Stimulating Factors (G-CSF). Requests for non-preferred short acting agents require trial of Zarxio and Nivestym in addition to meeting the clinical criteria detailed below.
- Fulphila and Udenyca are the preferred long acting Granulocyte Colony Stimulating Factors (G-CSF). Requests for non-preferred long acting agents require trial of Fulphila and Udenyca in addition to meeting the clinical criteria detailed below.

General Authorization Criteria for ALL Agents and Indications:

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

Additional Criteria Based on Indication:

- **Chemotherapy-Induced Febrile Neutropenia: (Neupogen, Neulasta, Fulphila, Udenyca, Granix, Leukine, Zarxio and Nivestym)**
- Member is receiving chemotherapy for a NON-myeloid cancer (for example, solid tumor, lymphoma)
    - For PRIMARY prophylaxis:
        - Member meets one of the following:
            - Chemotherapy regimen is given after bone marrow transplant; OR
            - Chemotherapy regimen has >20% risk of febrile neutropenia; OR
            - Chemotherapy regimen has 10%-20% risk of febrile neutropenia AND member has ANY of the following risk factors for febrile neutropenia:
                - age > 65 years
                - prior chemotherapy or radiation therapy
                - persistent neutropenia
                - bone marrow involvement by tumor

- Recent surgery and or open wounds
- Liver dysfunction (bilirubin > 2.0)
- Renal dysfunction (creatinine clearance (CRCL) <50)

- For SECONDARY prophylaxis (**Neupogen, Neulasta, Fulphila, Udenyca Granix, Leukine, Zarxio and Nivestym**): Member previously experienced febrile neutropenia from the same chemotherapy regimen and reducing or delaying chemotherapy dose may compromise treatment outcome
- For TREATMENT of febrile neutropenia **(Leukine, Neupogen, Zarxio and Nivestym**) in members who did NOT receive colony stimulating factor (CSFs) prophylaxis: Member has risk factors for poor outcomes resulting from febrile neutropenia (for example: age > 65, sepsis, severe neutropenia (absolute neutrophil count (ANC)< 100/mcL), current infection, hospitalized at onset of fever, prior episode of febrile neutropenia)

- **Severe chronic congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia: (Zarxio, Nivestym and Neupogen)**
  - Member has one of the following:
    - Evidence of inadequate bone marrow reserve (for example: recurrent fevers, splenomegaly, mucosal ulcers, abdominal pain)
    - High risk for developing serious bacterial infection (for example: primarily severe neutropenia, indwelling venous catheters, prior serious infections)
    - Current bacterial infection
- **Neutropenia related to Human Immunodeficiency Virus (HIV) or drug therapy; ganciclovir or zidovudine induced: (Zarxio, Nivestym, Neupogen, Leukine)**
  - Prescribed by, or in consultation with an Infectious Disease Specialist, Hematologist, or Human Immunodeficiency Virus (HIV) Specialist

- **Neupogen, Zarxio and Nivestym may also be approved if medically necessary for the following indications:**
  - Acute Myeloid Leukemia in members receiving induction or consolidation chemotherapy
  - Mobilization of hematopoietic progenitor cells before autologous stem cell transplant
  - Mobilization of hematopoietic progenitor cells in the donor before allogenic stem cell transplant
  - Treatment of acute radiation exposure in members who receive myelosuppressive doses of radiation at a dose of 2 gray (Gy)
  - Myelodysplastic Syndrome (MDS) or aplastic anemia in a member with an absolute neutrophil count (ANC) <500

- **Leukine may also be approved if medically necessary for the following indications:**
  - Acute Myeloid Leukemia after induction chemotherapy for members age 55 years or older
  - Bone marrow transplant failure or engraftment delay
  - Myeloid reconstitution after allogenic bone marrow transplant
  - Myeloid reconstitution after autologous bone marrow transplant in members with Hodgkin's disease, non-Hodgkin's lymphoma, or acute lymphocytic leukemia
  - Before and after autologous peripheral blood stem cell transplantation
  - Patients acutely exposed to myelosuppressive doses of radiation, administer once daily as subcutaneous injection.

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Initial Approval:

- Chemotherapy-induced neutropenia (primary or secondary prophylaxis):
  - Approve per cycle of chemotherapy:
    - Up to a 14 day supply for Neupogen, Zarxio, Nivestym, Granix, and Leukine
    - One (1) 6 mg dose of Neulasta, Fulphila, Udenyca no less than every 14 days
    - Include refills if number of cycles is provided
  - Treatment of neutropenia (for example: congenital, cyclic, or idiopathic, Human Immunodeficiency Virus (HIV), or after chemo + bone marrow transplant (BMT)):
    - Approve for 3 months
- For other indications
  - Up to six months or less

Renewal:

- Chemotherapy-induced neutropenia (primary or secondary prophylaxis):
  - Recent absolute neutrophil count (ANC) showing a response to therapy
  - Approve per cycle of chemotherapy:
    - Up to a 14 day supply for Neupogen, Zarxio, Nivestym, Granix and Leukine
    - One (1) 6 mg dose of Neulasta, Fulphila, Udenyca no less than every 14 days
    - Include refills if number of cycles is provided, or up to 12 months
- All other indications:
  - Recent absolute neutrophil count (ANC), complete blood count (CBC), and/or platelet counts
  - Approve up to one year

Additional Information:

Note: Neutropenia is defined as an absolute neutrophil count (ANC) of < 500 neutrophils/mcL or an absolute neutrophil count (ANC) of < 1000 neutrophils/mcL and a predicted decline to < than or equal to 500 neutrophils/mcL over the next 48 hours.

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

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Dosing Table:

Medication	Dosing	Available Dosage forms
Neupogen **Zarxio** **Nivestym**	• Febrile Neutropenia (FN) or acute myeloid leukemia (AML): 5 mcg/kg/day (Not given 24 hours before chemotherapy and 24 hours after) • Bone marrow transplant (BMT): 10 mcg/kg/day (given 24 hrs. after bone marrow transplant (BMT) and given for at least 24 hours) • Peripheral Blood Progenitor Cell (PBPC): 10 mcg/kg/day; at least 4 days before and up to 7 days • Severe Chronic Neutropenia: o Idiopathic neutropenia:1.2 mcg/kg/day o Cyclic neutropenia: 2.1 mcg/kg/day o Congenital neutropenia: 6 mcg/kg/day divided 2 times per day	Vials: • 300 mcg/mL, single-dose vial • 480 mcg/1.6 mL, single-dose vial Prefilled Syringe • 300 mcg/0.5 mL per syringe • 480 mcg/0.8 mL per syringe
Neulasta **Fulphila** **Udenyca**	• Febrile Neutropenia- 5mcg/kg/day Not given 24 hours before chemotherapy and 24 hours after chemotherapy. Given once per chemotherapy cycle	• 6 mg/0.6 mL, single-dose prefilled syringe • 6 mg/0.6 mL, single-dose prefilled syringe co-packaged with the On-body Injector (Neulasta Onpro kit).

Leukine	• Acute myeloid leukemia (AML): 250 mcg/m^2/day subcutaneous (SQ) or intravenous (IV) on day 11 or 4 days following the 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 BMT (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 Pediatric patients 15 kg to 40 kg: 10mcg/kg o Pediatric patientsPeripheral Blood Progenitor Cell (PBPC): 250mcg/m^2/day SQ or IV over 24 hours	• 500 mcg/mL vial • 250 mcg powder for injection
Granix	• Febrile Neutropenia (FN) 5mcg/kg/day subcutaneous (SQ) injection • Not given 24 hours before chemotherapy and 24 hours after chemotherapy	• 300 mcg/0.5 mL, single-use prefilled syringe • 480 mcg/0.8 mL, single-use prefilled syringe

References:

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13. Fulphila (pegfilgrastim-jmdb) [prescribing information]. Rockford, IL: Mylan Institutional LLC; June 2018
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15. Udenyca (pegfilgrastim-cbqv) [prescribing information]. Redwood City, CA: Coherus Biosciences; November 2018.

Table: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of 20% or Higher

Cancer Histology	Treatment Setting	Regimen
Acute Lymphoblastic Leukemia (ALL)	Induction	ALL induction regimens (see NCCN guidelines)
Bladder Cancer	Neoadjuvant, adjuvant, metastatic	MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)
	Prior adjuvant allowed	CBDCa/Pac (carboplatin, paclitaxel)
Breast Cancer	Metastatic or relapsed	Docetaxel + trastuzumab
	Adjuvant	Dose-dense AC followed by T (doxorubicin, cyclophosphamide, paclitaxel)
	Adjuvant	TAC (docetaxel, doxorubicin, cyclophosphamide)
	Metastatic (1st line)	AT (doxorubicin, docetaxel)
	Metastatic (2nd line)	Doc (docetaxel)
Esophageal and Gastric Cancers		Docetaxel/cisplatin/fluorouracil
Hodgkin Lymphoma		BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)
Kidney Cancer		Doxorubicin/gemcitabine

Non-Hodgkin's Lymphoma	Diffuse large B-cell lymphoma {DLBCL], peripheral T-cell lymphomas (PTCL], 2nd line	ICE (ifosfamide, carboplatin, etoposide)
		RICE (rituximab, ifosfamide, carboplatin, etoposide)
		CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
	DLBCL, 2nd line, refractory	MINE (mesna, ifosfamide, novantrone, etoposide)
	PTCL, DLBCL, 2nd line	DHAP (dexamethasone, cisplatin, cytarabine)
	DLBCL, PTCL, 2nd line, recurrent	ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine (Ara-C))
		HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)
	Relapsed	VAPEC-B (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin)
Melanoma	Advanced, metastatic, or recurrent	Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine)
	Advanced, metastatic, or recurrent	Dacarbazine-based combination with IL-2, interferon alpha (dacarbazine, cisplatin, vinblastine, IL-2, interferon alpha)
Ovarian Cancer		Topotecan
		Paclitaxel
		Docetaxel
Pancreatic Cancer	Advanced or metastatic	FOLFIRINOX (leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin)

Soft Tissue Sarcoma		MAID (mesna, doxorubicin, ifosfammide, dacarbazine)
		Doxorubicin
		Ifosfamide/doxorubicin
Small Cell Lung Cancer	Recurrent	Top (topotecan)
		CAV (cyclophosphamide, doxorubicin, vincristine)
Testicular cancer	Relapsed	VelP (vinblastine, ifosfamide, cisplatin)
		VIP (etoposide, ifosfamide, cisplatin)
		BEP (bleomycin, etoposide, cisplatin)
		TIP (paclitaxel, ifosfamide, cisplatin)

Source: Smith, et al., 2006; NCCN, 2016.

Table: Selected Chemotherapy Regimens with an Incidence of Febrile Neutropenia of 10% to 19%

Cancer Histology	**Treatment Setting**	**Regimen**
Occult primary - adenocarcinoma		Gemcitabine/docetaxel
Breast cancer		Docetaxel every 21 days
	Adjuvant	CMF classic (cyclophosphamide, methotrexate, fluorouracil)
	Adjuvant	CA (doxorubicin, cyclophosphamide) (60 mg/m2) (hospitalized)
	Adjuvant (taxane portion only)	AC (doxorubicin, cyclophosphamide) + sequential docetaxel
	Adjuvant	AC + sequential docetaxel + trastuzumab
	Metastatic (1st	A (doxorubicin) (75)

	line)	
	Metastatic (1st line)	AC (doxorubicin, cyclophosphamide)
	Metastatic (2nd line)	CapDoc (capecitabine, docetaxel)
		FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel
	Metastatic or relapsed	Paclitaxel every 21 days
		TC (docetaxel, cyclophosphamide)
Cervical Cancer		FOLFOX (fluorouracil, leucovorin, oxaliplatin)
Colorectal	Advanced	FL (fluorouracil, leucovorin)
	Advanced (one prior chemo allowed)	CPT-11 (irinotecan) (350 mg/m2 q 3 wk)
Esophageal and Gastric Cancers		Irinotecan/cisplatin
		Epirubicin/cisplatin/5-fluorouracil
		Epirubicin/cisplatin/capecitabine
Head and Neck	Induction	Cis/Doc/5-FU (cisplatin, docetaxel, 5-fluorouracil)
Multiple myeloma		DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophoaphamide/etoposide)
		DT-PACE + bortezomib (VTD-PACE)
Non-Hodgkin's lymphomas	AIDS-related NHL, Burkitt lymphoma, recurrent, otehr NHL subtypes	EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
	AIDS-related NHL, DLBCL, recurrent	EPOCH-IT chemotherapy

	DLBCL, PTCL, 2nd line	GDP (gemcitabine, dexamethasone, cisplatin)
	DLBCL, 2nd line, Burkitt lymphoma, other NHL subtypes	GDP (gemcitabine, dexamethasone, cisplatin) + rituximab
		FMR (fludarabine, mitoxantrone, rituximab)
		CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) including regimens with pegylated liposomal doxorubicin or mitoxantrone substituted for doxorubicin
Non-Small Cell Lung Cancer	Advanced/metastatic	Cisplatin/paclitaxel
	Adjuvant, advanced/metastatic	Cisplatin/vinorelbine
	Adjuvant, advanced/metastatic	Cisplatin/docetaxel
	Adjuvant, advanced/metastatic	Cisplatin/etoposide
	Adjuvant, advanced/metastatic	Carboplatin/paclitaxel
	Advanced/metastatic	Docetaxel
Ovarian Cancer		Carboplatin/docetaxel
Pancreatic Cancer		FOLFIRINOX
Prostate Cancer		Cabazitaxel
Small Cell Lung Cancer		Etoposide/carboplatin

Testicular Cancer		Etoposide/carboplatin
Uterine Sarcoma	Advanced or metastatic	Docetaxel