LifeWise

PHARMACY / MEDICAL POLICY – 5.01.551

Use of Granulocyte Colony-Stimulating Factors (G-CSF)

Effective Date:	Jan. 1, 2021	RELATED MEDICAL POLICIES:
Last Revised:	Dec. 17, 2020	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

People with certain cancers may be given drugs (chemotherapy) to treat their disease. A side effect of many chemotherapy drugs is destruction of or delay in making immune cells that fight infection. These cells are known as white blood cells, neutrophils, or granulocytes. Neutropenia means a lack of granulocytes (infection-fighting cells). People being treated for cancer may develop neutropenia and fever. When this happens, treatment with antibiotics in the hospital is often necessary in case there is a serious infection. In the 1980s scientists discovered a type of protein called granulocyte-colony stimulating factor (G-CSF) that stimulates the body to make more granulocytes. It has become a standard practice to give G-CSF drugs along with certain types of chemotherapy likely to cause neutropenia. These agents can also be given as part of a bone marrow or stem cell transplant or to treat some rare conditions. Recently new forms of these agents, which are less costly, have become available; studies show them to be equivalent. The newer agents, Granix® (tbo-filgrastim) and Nivestym® (filgrastim-aafi) are less costly and therefore are preferred for coverage. Granix® and Nivestym® do not need preapproval for coverage. All other G-CSF agents require preapproval. Depending on the diagnosis, using Granix® or Nivestym® may be necessary before one of the other drugs is covered.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can

be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Targeted Use	Medical Necessity
Patients treated with myelosuppressive anti-cancer regimens, at risk of severe febrile neutropenia to decrease the incidence of infection**	**Granix® (tbo-filgrastim) or Nivestym® (filgrastim-aafi) may be considered medically necessary as first-line therapy for adult and pediatric patients. Granix® (tbo-filgrastim) and Nivestym® (filgrastim-aafi) do not need preapproval for coverage.** **Neupogen® (filgrastim) and Zarxio® (filgrastim-sndz) may be considered medically necessary as:** • Second-line therapy when documentation for one of the following is provided: ○ Granix® (tbo-filgrastim) or Nivestym® (filgrastim-aafi) has been tried and failed **OR** ○ There is a contraindication to the use of Granix® (tbo-filgrastim) and Nivestym® (filgrastim-aafi) **Udenyca® (pegfilgrastim-cbqv) and Ziextenzo® (pegfilgrastim-bmez) may be considered medically necessary for:** • Treatment of patients less than 18 years of age **OR** • Treatment of patients 18 years of age or older as second-line therapy when documentation for one of the following is provided: ○ Granix® (tbo-filgrastim) or Nivestym® (filgrastim-aafi) has been tried and failed **OR** ○ There is a contraindication to the use of Granix® (tbo-filgrastim) and Nivestym® (filgrastim-aafi)

Targeted Use	Medical Necessity
	OR ○ A valid medical rationale is provided for why self-injection or home nursing cannot be performed **Neulasta® (pegfilgrastim) / Neulasta Onpro®, Fulphila® (pegfilgrastim-jmdb), and Nyvepria™ (pegfilgrastim-apgf) may be considered medically necessary for:** • Treatment of patients less than 18 years of age **AND** • As second-line therapy when documentation for one of the following is provided: ○ Udenyca® (pegfilgrastim-cbqv) or Ziextenzo® (pegfilgrastim-bmez) has been tried and failed **OR** ○ There is a contraindication to the use of Udenyca® (pegfilgrastim-cbqv) and Ziextenzo® (pegfilgrastim-bmez) **OR** • Treatment of patients 18 years of age or older as third-line therapy when documentation for the following is provided: ○ Granix® (tbo-filgrastim) or Nivestym® (filgrastim-aafi) has been tried and failed **AND** ○ Udenyca® (pegfilgrastim-cbqv) or Ziextenzo® (pegfilgrastim-bmez) has been tried and failed **OR** ○ There is a contraindication to the use of Granix® (tbo-filgrastim), Nivestym® (filgrastim-aafi), Udenyca® (pegfilgrastim-cbqv) and Ziextenzo® (pegfilgrastim-bmez) ****For purposes of this policy, the following types of patients are considered to be at risk of severe febrile neutropenia:** 1. Patients that have experienced febrile neutropenia during a previous cycle of treatment with the current chemotherapy regimen **OR**

Targeted Use	Medical Necessity
	2. Patients receiving chemotherapy regimen that is expected to result in a 20 % or higher incidence of FN, based on guidelines from the American Society of Clinical Oncology (see **Appendix**, Smith et al, 2006) **OR** 3. Patients with bone marrow impairment **OR** 4. Patients that have received 2 or more prior chemotherapy regimens or extensive radiation **OR** 5. Patients with other serious comorbidities (reviewed on a case basis) **Note**: Colony-stimulating factors should not be routinely used for afebrile neutropenia (Smith et al, 2006).
Patients undergoing autologous peripheral blood progenitor cell collection and therapy	**Nivestym® (filgrastim-aafi) may be considered medically necessary as first-line therapy for adult and pediatric patients. Nivestym® (filgrastim-aafi) does not need preapproval for coverage.** **Neupogen® (filgrastim) and Zarxio® (filgrastim-sndz) may be considered medically necessary as:** • Second-line therapy when documentation for one of the following is provided: ○ Nivestym® (filgrastim-aafi) has been tried and failed **OR** ○ There is a contraindication to the use of Nivestym® (filgrastim-aafi)
Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)	**Neupogen® (filgrastim) and Neulasta® (pegfilgrastim) / Neulasta Onpro® may be considered medically necessary as first-line therapy for adult and pediatric patients.**
Combination treatment with chemotherapy regimens	**Udenyca® (pegfilgrastim-cbqv) and Ziextenzo® (pegfilgrastim-bmez) may be considered medically necessary as first-line therapy when used in combination**

Targeted Use	Medical Necessity
	with chemotherapy regimens where pegfilgrastim was the only G-CSF product used in published clinical trials. • When using Udenyca® (pegfilgrastim-cbqv) and Ziextenzo® (pegfilgrastim-bmez) for this reason, the requesting provider should provide article citations supporting the request. **Neulasta® (pegfilgrastim) / Neulasta Onpro®, Fulphila® (pegfilgrastim-jmdb), and Nyvepria™ (pegfilgrastim-apgf) may be considered medically necessary as second-line therapy when used in combination with chemotherapy regimens where pegfilgrastim was the only G-CSF product used in published clinical trials when documentation for one of the following is provided:** • Udenyca® (pegfilgrastim-cbqv) or Ziextenzo® (pegfilgrastim-bmez) has been tried and failed **OR** • There is a contraindication to the use of Udenyca® (pegfilgrastim-cbqv) and Ziextenzo® (pegfilgrastim-bmez)

Targeted Use	Investigational
Not listed in this policy	**Any other uses of the following G-CSF products not addressed in this policy are considered investigational:** • Fulphila® (pegfilgrastim-jmdb) • Granix® (tbo-filgrastim) • Neulasta® (pegfilgrastim) / Neulasta Onpro® • Neupogen® (filgrastim) • Nivestym® (filgrastim-aafi) • Nyvepria™ (pegfilgrastim-apgf) • Udenyca® (pegfilgrastim-cbqv) • Zarxio® (Filgrastim-sndz) • Ziextenzo® (pegfilgrastim-bmez)

Length of Approval	
Approval	**Criteria**
Initial authorization	**Drugs listed in policy may be approved up to 12 months.**

Length of Approval	
Approval	**Criteria**
Re-authorization criteria	**Future re-authorization may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the patient continues to show a positive clinical response to therapy.**

Documentation Requirements
The patient's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, targeted use of G-CSF product, relevant history, physical evaluation, and medication history

Coding

Code	Description
CPT	
96377	Application of on-body injector (includes cannula insertion) for timed subcutaneous injection (Neulasta Onpro®) (Both injector and drug are inclusive)
HCPCS	
J1442	Injection, filgrastim (G-CSF) (Neupogen®), 1 microgram
J2505	Injection, pegfilgrastim (Neulasta®), 6 mg
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio®), 1 microgram
Q5108	Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila®), 0.5 mg
Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca®), 0.5 mg
Q5120	Injection, pegfilgrastim-bmez, biosimilar, (Ziextenzo®), 0.5 mg
Q5122	Injection, pegfilgrastim-apgf, biosimilar, (nyvepria), 0.5 mg (new code effective 1/1/21)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

This policy addresses the following granulocyte colony-stimulating factors:

Granix® (tbo-filgrastim)

A non-glycosylated recombinant methionyl human granulocyte colony-stimulating growth factor (r-metHuG-CSF) manufactured by recombinant DNA technology using the bacterium strain E coli K802. It is identical in amino acid sequence to filgrastim but is produced by a different manufacturer using a slightly different process. Granix® (tbo-filgrastim) was reviewed by the FDA independent of the original BLA for filgrastim and was assigned the prefix "Tbo" to differentiate the two. Both are produced in vitro using genetically engineered strains of E. coli. Granix® (tbo-filgrastim) is indicated to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia because it was independently labelled as a separate drug by FDA it has slightly different labelled indications from Neupogen, however, it has identical labelling and indications for FN.

Nivestym® (filgrastim-aafi)

Nivestym® (filgrastim-aafi) is a biosimilar to Neupogen® (filgrastim). Filgrastim-aafi is a 175 amino acid human G-CSF manufactured by recombinant DNA technology. Nivestym® is produced by E coli bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E coli. Because Nivestym® is produced in E coli, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

Neupogen® (filgrastim)

A recombinant human granulocyte colony-stimulating factor produced by Amgen, Inc. It is recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF, which is a 175 amino acid protein identical to the endogenous growth factor except for an inserted N-terminal methionine and the lack of glycosylation). Neupogen® (filgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-

myeloid malignancies receiving myelosuppressive anti-cancer drugs in one of the following categories:

1. Cancer patients receiving myelosuppressive chemotherapy
2. Patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy
3. Cancer patients receiving bone marrow transplantation
4. Patients undergoing Peripheral Blood Progenitor Cell Collection and Therapy
5. Patients with Severe Chronic Neutropenia

Patients in these categories are associated with a significant incidence of severe febrile neutropenia (FN).

Zarxio® (filgrastim-sndz)

A 175 amino acid human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology. Zarxio® (filgrastim-sndz) is produced by Escherichia coli (E coli) bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. Zarxio has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E coli. Because Zarxio is produced in E coli, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

Neulasta® (pegfilgrastim) / Neulasta Onpro®

A covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Neulasta® (pegfilgrastim) / Neulasta Onpro® is indicated to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia.

Fulphila® (pegfilgrastim-jmdb)

Fulphila® (pegfilgrastim-jmdb) is a biosimilar to Neulasta® (pegfilgrastim). Pegfilgrastim-jmdb is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a strain of E coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim-jmdb a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF.

Nyvepria™ (pegfilgrastim-apgf)

Nyvepria™ (pegfilgrastim-apgf) is a biosimilar to Neulasta® (pegfilgrastim). Pegfilgrastim-apgf is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a strain of E. coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim-apgf, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF. The average molecular weight of pegfilgrastim-apgf is approximately 39 kD.

Udenyca® (pegfilgrastim-cbqv)

Udenyca® (pegfilgrastim-cbqv) is a biosimilar to Neulasta® (pegfilgrastim). Pegfilgrastim-cbqv is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a strain of E coli transformed with a genetically engineered plasmid containing the human G-CSF gene. During the pegfilgrastim-cbqv manufacturing process, fermentation is carried out in nutrient medium containing the antibiotic kanamycin. However, kanamycin is cleared in the manufacturing process and is not detectable in the final product. To produce pegfilgrastim-cbqv, a 20 kDa monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF.

Ziextenzo® (pegfilgrastim-bmez)

Ziextenzo® (pegfilgrastim-bmez) is a biosimilar to Neulasta® (pegfilgrastim). Pegfilgrastim-bmez is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a strain of E coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim-bmez, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF. The average molecular weight of pegfilgrastim-bmez is approximately 39 kD.

Biosimilars

As filgrastim and pegfilgrastim patents expire a variety of biosimilar products entered the market. Zarxio® was the first biosimilar filgrastim product, followed by Nivestym®. Fulphila® is the first biosimilar pegfilgrastim product followed by Udenyca®, Ziextenzo® and then Nyvepria™. Subsequent biosimilar products will be added to this policy as they appear.

Table 1. Summary of Labeled Indications for G-CSF Products

	Myelosuppressive Chemotherapy	Acute Myeloid Leukemia	Bone Marrow Transplant	Progenitor Cell Collection	Severe Chronic Neutropenia	Acute Radiation Syndrome
Fulphila®	X					
Granix®	X					
Neulasta®	X					X
Neupogen®	X	X	X	X	X	X
Nivestym®	X	X	X	X	X	
Nyvepria™	X					
Udenyca®	X					
Zarxio®	X	X	X	X	X	
Ziextenzo®	X					

Contraindications

Fulphila®, Granix®, Neulasta®, Neupogen®, Nivestym®, Nyvepria™, Udenyca®, Zarxio® and Ziextenzo® are contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim products.

Benefit Application

Fulphila®, Granix®, Neulasta®, Neupogen®, Nivestym®, Nyvepria™, Udenyca®, Zarxio® and Ziextenzo® may be managed under either the medical benefit (if administered by a provider) or pharmacy benefit (if administered by the patient or a nonprofessional caregiver).

Evidence Review

Efficacy

Neupogen® (filgrastim) has been shown to be safe and effective in accelerating the recovery of neutrophil counts following a variety of chemotherapy regimens. In a phase III clinical trial in small cell lung cancer, the benefits of filgrastim over placebo were shown to be prevention of infection as manifested by febrile neutropenia, decreased hospitalization, and decreased IV antibiotic usage. No difference in survival or disease progression was demonstrated. Filgrastim is also indicated for use in adjunct to acute myeloid leukemia (AML) chemotherapy induction and consolidation. In a phase III clinical trial, it was found to effectively reduce the duration of neutropenia, leading to significant clinical benefits by reducing the duration of fever; requirement for parenteral anti-infectives; and the duration of hospitalization. Filgrastim also has an indication for use in severe chronic neutropenia, in which a phase III clinical trial showed that the use of filgrastim resulted in a stimulation of bone marrow production and maturation of neutrophils, an increase in circulating neutrophils, and a reduction in the infection-related events. Filgrastim is also indicated for the use of stem cell harvest in donors.

Granix® (tbo-filgrastim) has been shown to be superior to placebo in duration of severe neutropenia (DSN) with a statistically significant reduction in DSN (1.1 days vs. 3.8 days, $p < 0.0001$). These results are from a phase III clinical trial in chemotherapy-naïve patients with high-risk stage II, stage III, or stage IV breast cancer.

Neulasta® (pegfilgrastim) has been shown safe and effective in accelerating the recovery of neutrophil counts. In a phase III study comparing pegfilgrastim to placebo, the incidence of hospitalizations (1% vs. 14%) and IV anti-infective use (2% vs. 10%) for the treatment of febrile neutropenia was lower in the pegfilgrastim treated patients compared to the placebo treated patients.

Comparative Effectiveness

In a Phase III study comparing pegfilgrastim to filgrastim as support for commonly used chemotherapy regimens, a single subcutaneous injection of pegfilgrastim provided adequate and safe neutrophil support comparable with daily subcutaneous injections of filgrastim in patients receiving commonly used standard-dose mild-to-moderate myelosuppressive chemotherapy regimens.

A Phase III clinical trial comparing pegfilgrastim to filgrastim for cytokine-alone mobilization of autologous hematopoietic stem and progenitor cells found that the total CD34+ cell yield was equivalent for both filgrastim- and pegfilgrastim-mobilized patients (80% vs. 91%, $p = 0.44$).

In a trial that compared fixed dose pegfilgrastim to daily filgrastim following autologous stem cell transplantations, it was found that there was no difference in outcomes in terms of safety and efficacy in a single dose of pegfilgrastim compared to 8 days of filgrastim.

In a single-blind, randomized, crossover trial comparing tbo-filgrastim to filgrastim, equivalence was demonstrated for the serum concentration profile, for the ANC profile, and for the CD34+ cell count, which is a marker for the ability of the GCSF to mobilize stem cells.

Safety

In clinical trials, the most common adverse events for filgrastim and peg-filgrastim was bone pain, which is often severe enough to require opioid analgesia. All three agents carry the risk of more serious adverse events, such as: splenic rupture, acute respiratory distress syndrome, serious allergic reactions, precipitation of severe sickle cell crisis in patients with sickle cell disorders, and the potential for tumor growth stimulatory effects on malignant cells.

Choosing Wisely Guidelines

ASCO guidelines recommend using white cell stimulating factors when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen, is greater than 20 percent and equally effective treatment programs that do not require white cell stimulating factors are unavailable (see **Appendix**).

Exceptions should be made when using regimens that have a lower chance of causing febrile neutropenia if it is determined that the patient is at high risk for this complication (due to age, medical history, or disease characteristics).

2015 Update

Added criteria and description for Zarxio® (filgrastim-sndz), a biosimilar to Neupogen that was recently approved by the FDA. A literature search from July 1, 2014, through October 31, 2015, did not identify any new evidence that would change the criteria for Neupogen, Neulasta, or Granix. This policy was reviewed by the Pharmacy and Therapeutics Committee November 19, 2015.

2016 Update

A literature search from July 1, 2015, through December 31, 2016, did not identify any new evidence that would change policy coverage.

2018 Update

A literature search from January 1, 2017, through January 30, 2018, did not identify any new evidence that would change policy coverage.

2019 Update

A literature search from January 1, 2018, through February 28, 2019, did not identify any new evidence that would change policy coverage. Updated references supporting interchangeability of biosimilars.

2020 Update

Reviewed prescribing information for all drugs listed in policy and conducted a literature search from January 1, 2019, through December 31, 2019. No new evidence was identified that would change coverage criteria. Added coverage criteria for Ziextenzo® (pegfilgrastim-bmez) which is a biosimilar to Neulasta® (pegfilgrastim).

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Appendix

Regimens with Predicted Risk of Febrile Neutropenia Greater than 20%

Regimen	Acronym	FN (%)	Cancer
Carboplatin + Paclitaxel		21	Bladder
Methotrexate + Vinblastine + Doxorubicin + Cisplatin	MVAC	> 20	Bladder
Docetaxel		21	Breast
Docetaxel + Trastuzumab		> 20	Breast
Dose-dense Doxorubicin + Cyclophosphamide followed by Paclitaxel	DD AC followed by T	> 20	Breast
Doxorubicin + Cyclophosphamide followed by Docetaxel	AC followed by Docetaxel	5-25	Breast
Docetaxel followed by Doxorubicin + Cyclophosphamide	Docetaxel followed by AC	40	Breast
Doxorubicin + Docetaxel		33-48	Breast
Doxorubicin + Paclitaxel		21-32	Breast
Docetaxel + Doxorubicin + Cyclophosphamide	TAC	22-25	Breast
Dose-dense Cyclophosphamide + Epirubicin + Fluorouracil	DD FEC	71	Breast

Regimen	Acronym	FN (%)	Cancer
Dose-dense Doxorubicin followed by Paclitaxel followed by Cyclophosphamide		> 20	Breast
Dose-dense Epirubicin + Cyclophosphamide		> 20	Breast
Cyclophosphamide + Epirubicin + Fluorouracil + Docetaxel	FEC-D	25-46	Breast
Fractionated cyclophosphamide + Vincristine + Doxorubicin + Dexamethasone + Rituximab	Hyper CVAD + Rituximab	> 20	Burkitt's Lymphoma
Paclitaxel + Cisplatin		28	Cervical
Docetaxel + Cisplatin + Fluorouracil		> 20	Esophageal/Gastric
Bleomycin + Vincristine + Cisplatin followed by Cisplatin + Ifosfamide + Etoposide	BOP followed by VIP	46	Germ Cell
Vinblastine + Ifosfamide + Cisplatin	VeIP	67-71	Germ Cell
Paclitaxel + Ifosfamide + Carboplatin	TIC	30	Head & Neck
Bleomycin + Etoposide + Doxorubicin + Cyclophosphamide + Vincristine + Procarbazine + Prednisone	BEACOPP	54	Hodgkin's
Doxorubicin + Bleomycin + Vinblastine +Dacarbazine	ABVD	> 20	Hodgkin's
Cyclophosphamide +Epirubicin + Fluorouracil	CEC	48	Hodgkin's
Ifosfamide + Mesna + Gemcitabine + Vinorelbine	IGEV	28	Hodgkin's
Doxorubicin + Gemcitabine		> 20	Kidney
Topotecan		28	Lung
Cyclophosphamide + Doxorubicin + Vincristine		26	Lung
Dacarbazine + Cisplatin + Vinblastine		> 20	Melanoma
Dacarbazine + Cisplatin + Vinblastine + IL-2, interferon alfa		> 20	Melanoma
Leucovorin-primed Fluorouracil	LVFU	20	Metastatic gastric cancer
Leucovorin-primed Fluorouracil + Cisplatin	LVFU-cisplatin	40	Metastatic gastric cancer
Leucovorin-primed Fluorouracil + Irinotecan	LVFU-irinotecan	24	Metastatic gastric cancer
Docetaxel + Cisplatin + Fluorouracil	DCF	29	Metastatic gastric cancer

Regimen	Acronym	FN (%)	Cancer
Docetaxel + Cyclophosphamide	TC	21	Metastatic gastric cancer
Docetaxel + Cyclophosphamide + Fluorouracil	TCF	41	Metastatic gastric cancer
Antithymocyte globulin, rabbit/cyclosporine		> 20	Myelodysplastic
Decitabine		> 20	Myelodysplastic
Cyclophosphamide + Fludarabine + Alemtuzumab + Rituximab	CFAR	> 20	NHL
Dose-dense Cyclophosphamide + Doxorubicin + Vincristine + Prednisone	CHOP-14	> 20	NHL
Rituximab + Dose-dense Cyclophosphamide + Doxorubicin + Vincristine + Prednisone	R-CHOP-14	> 20	NHL
Mesna + Ifosfamide + Novantrone + Etoposide	MINE	> 20	NHL
Cisplatin + Cytarabine + Dexamthasone	DHAP	48	NHL/CLL
Etoposide + methylprednisolone + Cytarabine + Cisplatin	ESHAP	30-64	NHL/CLL
Rituximab + Etoposide + methylprednisolone + Cytarabine + Cisplatin	R-ESHAP	33.5	NHL/CLL
Cyclophosphamide + Doxorubicin + Vincristine + Prednisone	CHOP-21	17-50	NHL/CLL
Dose-dense Vincristine + Doxorubicin + Prednisolone + Etoposide + Cyclophosphamide + Bleomycin	DD VAPEC-B	44	NHL/CLL
Dose-dense Doxorubicin or Mitoxantrone + Cyclophosphamide + Vindesine + Bleomycin	DD ACBVP	78	NHL/CLL
Ifosfamide + Carboplatin + Etoposide	ICE	11.5-24	NHL/CLL
Rituximab + Ifosfamide + Carboplatin + Etoposide	R-ICE	11.5-24	NHL/CLL
Mechlorethamine + Doxorubicin + Vinblastine + Vincristine + Bleomycin + Etoposide + Prednisolone	Stanford V	25	NHL/CLL
Mechlorethamine + Vincristine + Procarbazine + Prednisone + Etoposide + Bleomycin + Vinblastine + Lomustine + Doxorubicin + Vindesine	MOPPEB-VCAD	49	NHL/CLL
Fludarabine + Cyclophosphamide	FC	35	NHL/CLL
Fludarabine + Cyclophosphamide + Rituximab	FCR	33.7	NHL/CLL
Docetaxel + Carboplatin		26	NSCLC

Regimen	Acronym	FN (%)	Cancer
Etoposide + Cisplatin		54	NSCLC
Cisplatin + Vinorelbine + Cetuximab		22	NSCLC
Vinorelbine + Ifosfamide + Gemcitabine	VIG	25	NSCLC
Topotecan		> 20	Ovarian
Docetaxel		33	Ovarian
Paclitaxel		22	Ovarian
Doxorubicin + Cyclophosphamide + Etoposide	ACE	24-57	SCLC
Topotecan		28	SCLC
Ifosfamide + Carboplatin + Etoposide	ICE	24	SCLC
Vincristine + Ifosfamide + Carboplatin + Etoposide	VICE	70	SCLC
Dose-dense Doxorubicin + Cyclophosphamide + Etoposide	DD ACE	34-56	SCLC
Dose-dense Ifosfamide + Carboplatin + Etoposide	DD ICE	> 20	SCLC
Dose-dense Cyclophosphamide + Doxorubicin + Vincristine followed by Cisplatin + Etoposide	DD CAV followed by PE	> 20	SCLC
Mesna + Doxorubicin + Ifosfamide + Dacarbazine	MAID	> 20	Soft Tissue Sarcoma
Doxorubicin		> 20	Soft Tissue Sarcoma
Ifosfamide + Doxorubicin		> 20	Soft Tissue Sarcoma
Vinblastine + Ifosfamide + Cisplatin	VeIP	> 20	Testicular
Etoposide + Ifosfamide + Cisplatin	VIP	> 20	Testicular
Bleomycin + Etoposide + Cisplatin	BEP	> 20	Testicular
Paclitaxel + Ifosfamide + Cisplatin	TIP	> 20	Testicular
Paclitaxel + Carboplatin		25	Urothelial
Methotrexate + Vinblastine + Doxorubicin + Cisplatin	MVAC	26	Urothelial
Dose-dense Methotrexate + Vinblastine + Doxorubicin + Cisplatin	DD MVAC	> 20	Urothelial

Source: Smith, 2006

History

Date	Comments
03/10/14	New policy. This policy is added to the Prescription Drug section and covers three granulocyte colony-stimulating factors: tbo-filgrastim (Granix®), filgrastim (Neupogen®) and pegfilgrastim (Neulasta®). All are considered medically necessary when criteria are met for conditions and per treatment guidelines outline in this policy. Policy approved with a hold for provider notification; it will be effective August 30, 2014.
08/11/14	Coding update. HCPCS codes J1442, J1446 and J2505 added to the policy.
10/13/14	Interim update. Policy reformatted to clarify details of step therapy in the use of GCSF; criteria added for making exceptions due to geographical issues.
02/10/15	Coding update. HCPCS code J1446 removed from policy; this is not being reviewed at this time.
12/08/15	Annual Review. Policy updated with literature review. Filgrastim-sndz (Zarxio) added to the medical necessity policy statements. Reviewed and approved by P&T Committee November 2015. Added HCPCS code Q5101.
02/09/16	Interim Review. Policy scope clarified to apply only to adults, age 18 and over.
10/01/16	Policy moved into new format; no change to policy statements.
04/01/17	Annual Review, approved March 14, 2017. No changes to criteria made. Added a new reference to the bibliography section (#15).
03/01/18	Annual Review, approved February 27, 2018. Minor change made to criteria. Deletion of first cycle of chemotherapy within the criteria. HCPCS code J1447 added to policy.
03/09/18	Coding update, added CPT code 96377.
04/01/18	Interim Review, approved March 20, 2018. Added "Neulasta Onpro®" for clarity.
10/01/18	Interim Review, approved September 21, 2018. Added Fulphila (pegfilgrastim-jmdb) criteria. Added Nivestym (filgrastim-aafi) criteria and contraindications. Added new HCPCS code Q5108 (new code effective 10/1/18).
01/01/19	Interim Review, approved December 19, 2018. Added Udenyca (pegfilgrastim-cbqv) criteria. Added use of Nivestym (filgrastim-aafi) as qualifier to second-line therapy. Added new HCPS code Q5110 (new code effective 1/1/19).
04/01/19	Annual Review, approved March 19, 2019. Literature search 1/1/18 – 2/28/19. No changes to policy. Updated references.
06/01/19	Coding update, added HCPCS code Q5111 (new code effective 1/1/19).
09/01/19	Interim Review, approved August 13, 2019. Added for targeted uses patients undergoing autologous peripheral blood progenitor cell collection and patients acutely exposed to myelosuppressive doses of radiation. Removed reference to Geographic Challenge and expanded to a valid medical rationale for why self-injection or home nursing cannot be performed.

Date	Comments
02/01/20	Annual Review, approved January 9, 2020. Added coverage criteria for Ziextenzo (pegfilgrastim-bmez) which is a biosimilar to Neulasta (pegfilgrastim). Added HCPCS code J3590 to report Ziextenzo.
04/01/20	Coding update. Added HCPCS code C9058, removed HCPCS code J3590.
07/01/20	Coding update. Added HCPCS code Q5120, removed HCPCS code C9058.
08/01/20	Interim Review, approved July 23, 2020. Added coverage criteria for Nyvepria (pegfilgrastim-apgf) which is a biosimilar to Neulasta (pegfilgrastim).
10/01/20	Interim Review, approved September 8, 2020, effective January 1, 2021. Changed policy title from "Granulocyte Colony-Stimulating Factor (G-CSF) Use in Adult Patients" to "Use of Granulocyte Colony-Stimulating Factors (G-CSF)". Added Udenyca (pegfilgrastim-cbqv) and Ziextenzo (pegfilgrastim-bmez) as first-line long-acting GCSF products in patients < 18 years of age. Updated coverage criteria for Neulasta (pegfilgrastim) / Neulasta Onpro, Fulphila (pegfilgrastim-jmdb), and Nyvepria (pegfilgrastim-apgf) to be second-line long-acting GCSF products in patients < 18 years of age and as third-line GCSF products in patients 18 years of age or older when being used to treat patients at risk of severe febrile neutropenia. Policy updates become effective for dates of service on or after January [Date], 2021, after 90-day provider notification. Added HCPCS J3590.
01/01/21	Coding update. Removed HCPCS codes J1447, J3590 and added Q5110. Added HCPCS Q5122.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-596-3440 (TTY: 711).

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 800-596-3440 (TTY: 711).

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注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。800-596-3440（TTY:711）まで、お電話にてご連絡ください。

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 800-596-3440 (رقم هاتف الصم والبكم: 711).

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XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 800-596-3440 (TTY: 711).

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เรียน: ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-596-3440 (TTY: 711).

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