PREMERA HMO

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PHARMACY / MEDICAL POLICY – 5.01.551

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

Effective Date:	**July. 1, 2025***	RELATED MEDICAL POLICIES:
Last Revised:	Feb. 11, 2025	None
Replaces:	N/A	
*Click here to view the current policy.		

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | APPENDIX | HISTORY

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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

Febrile Neutropenia (FN) with Anti-Cancer Regimens	
First-line	
Filgrastim Agents	
Granix (tbo-filgrastim) SC Nivestym (filgrastim-aafi) IV/SC	
Second-Line	
Filgrastim Agents	**Pegfilgrastim Agents**
Neupogen (filgrastim) IV/SC Releuko (filgrastim-ayow) IV/SC Zarxio (filgrastim-sndz) IV/SC Nypozi (filgrastim-txid) IV/SC	Fulphila (pegfilgrastim-jmdb)* SC Udenyca (pegfilgrastim-cbqv)* SC Udenyca Onbody (pegfilgrastim-cbqv)* SC
Third-Line	
Pegfilgrastim Agents	**Other Agents**
Fylnetra (pegfilgrastim-pbbk) SC Neulasta (pegfilgrastim) SC Neulasta Onpro (pegfilgrastim) SC Nyvepria (pegfilgrastim-apgf) SC Stimufend (pegfilgrastim-fpgk) SC Ziextenzo (pegfilgrastim-bmez) SC	Rolvedon (eflapegrastim-xnst) SC Ryzneuta (efbemalenograstim alfa-vuxw) SC

*Note: Considered first-line for individuals less than 18 years of age

Agent	Medical Necessity, FN with Anti-Cancer Regimens
• **Granix (tbo-filgrastim)** • **Nivestym (filgrastim-aafi)**	**Granix (tbo-filgrastim) or Nivestym (filgrastim-aafi) may be considered medically necessary as first-line therapy to decrease the incidence of infection for adult and pediatric individuals treated with myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia.**

Agent	Medical Necessity, FN with Anti-Cancer Regimens
	Note: Granix (tbo-filgrastim) and Nivestym (filgrastim-aafi) do not need preapproval for coverage.
• **Neupogen (filgrastim)** • **Nypozi (filgrastim-txid)** • **Releuko (filgrastim-ayow)** • **Zarxio (filgrastim-sndz)**	**Neupogen (filgrastim), Nypozi (filgrastim-txid), Releuko (filgrastim-ayow), and Zarxio (filgrastim-sndz) may be considered medically necessary to decrease the incidence of infection for adult and pediatric individuals treated with myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia when all the following are met:** • Documentation is provided that the individual has tried and failed Granix (tbo-filgrastim) or Nivestym (filgrastim-aafi) **OR** • There is a contraindication to the use of Granix (tbo-filgrastim) AND Nivestym (filgrastim-aafi)
• **Fulphila (pegfilgrastim-jmdb)** • **Udenyca (pegfilgrastim-cbqv** • **Udenyca Onbody (pegfilgrastim-cbqv)**	**Fulphila (pegfilgrastim-jmdb), Udenyca (pegfilgrastim-cbqv), and Udenyca Onbody (pegfilgrastim-cbqv) may be considered medically necessary to decrease the incidence of infection for adults treated with myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia when all the following are met:** • The individual is aged 18 years or older **AND** • Documentation is provided that the individual has tried and failed Granix (tbo-filgrastim) or Nivestym (filgrastim-aafi) **OR** • Documentation is provided that the individual has a contraindication to the use of Granix (tbo-filgrastim) AND Nivestym (filgrastim-aafi) **OR** • Documentation of a valid medical rationale is provided for why self-injection or home nursing cannot be performed with Granix (tbo-filgrastim) AND Nivestym (filgrastim-aafi) **Fulphila (pegfilgrastim-jmdb), Udenyca (pegfilgrastim-cbqv), and Udenyca Onbody (pegfilgrastim-cbqv) may be considered medically necessary as first-line therapy to decrease the incidence of infection for individuals less than**

Agent	Medical Necessity, FN with Anti-Cancer Regimens
	18 years of age treated with myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia.
• **Fylnetra (pegfilgrastim-pbbk)** • **Neulasta (pegfilgrastim)** • **Neulasta Onpro (pegfilgrastim)** • **Nyvepria (pegfilgrastim-apgf)** • **Stimufend (pegfilgrastim-fpgk)** • **Ziextenzo (pegfilgrastim-bmez)**	**Fylnetra (pegfilgrastim-pbbk), Neulasta (pegfilgrastim), Neulasta Onpro (pegfilgrastim), Nyvepria (pegfilgrastim-apgf), Stimufend (pegfilgrastim-fpgk), and Ziextenzo (pegfilgrastim-bmez) may be considered medically necessary to decrease the incidence of infection for adults treated with myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia when all the following are met:** • The individual is aged 18 years or older **AND** • Documentation is provided that the individual has tried and failed Granix (tbo-filgrastim) or Nivestym (filgrastim-aafi) **OR** • Documentation is provided that the individual has a contraindication to the use of Granix (tbo-filgrastim) AND Nivestym (filgrastim-aafi) **AND** Documentation is provided that the individual has tried and failed Fulphila (pegfilgrastim-jmdb) AND Udenyca (pegfilgrastim-cbqv) or Udenyca Onbody (pegfilgrastim-cbqv) **OR** • Documentation is provided that the individual has a contraindication to the use of Fulphila (pegfilgrastim-jmdb) AND Udenyca (pegfilgrastim-cbqv) or Udenyca Onbody (pegfilgrastim-cbqv) **Fylnetra (pegfilgrastim-pbbk), Neulasta (pegfilgrastim), Neulasta Onpro (pegfilgrastim), Nyvepria (pegfilgrastim-apgf), Stimufend (pegfilgrastim-fpgk), and Ziextenzo (pegfilgrastim-bmez) may be considered medically necessary to decrease the incidence of infection for individuals less than 18 years of age treated with**

Agent	Medical Necessity, FN with Anti-Cancer Regimens
	myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia when all the following are met: • The individual is aged less than 18 years **AND** • Documentation is provided that the individual has tried and failed Fulphila (pegfilgrastim-jmdb) AND Udenyca (pegfilgrastim-cbqv) or Udenyca Onbody (pegfilgrastim-cbqv) **OR** • Documentation is provided that the individual has a contraindication to the use of Fulphila (pegfilgrastim-jmdb) AND Udenyca (pegfilgrastim-cbqv) or Udenyca Onbody (pegfilgrastim-cbqv)
• **Rolvedon (eflapegrastim-xnst)** • **Ryzneuta (efbemalenograstim alfa-vuxw)**	**Rolvedon (eflapegrastim-xnst) and Ryzneuta (efbemalenograstim alfa-vuxw) may be considered medically necessary to decrease the incidence of infection for adults treated with myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia when all the following are met:** • The individual is aged 18 years or older **AND** • Documentation is provided that the individual has tried and failed Granix (tbo-filgrastim) or Nivestym (filgrastim-aafi) **OR** • Documentation is provided that the individual has a contraindication to the use of Granix (tbo-filgrastim) AND Nivestym (filgrastim-aafi) **AND** Documentation is provided that the individual has tried and failed Fulphila (pegfilgrastim-jmdb) AND Udenyca (pegfilgrastim-cbqv) or Udenyca Onbody (pegfilgrastim-cbqv) **OR** • Documentation is provided that the individual has a contraindication to the use of Fulphila (pegfilgrastim-jmdb) AND Udenyca (pegfilgrastim-cbqv) or Udenyca Onbody (pegfilgrastim-cbqv)

Agent	Medical Necessity, Other Uses
• **Nivestym (filgrastim-aafi)** • **Neupogen (filgrastim)** • **Nypozi (filgrastim-txid)** • **Zarxio (filgrastim-sndz)**	**Nivestym (filgrastim-aafi) may be considered medically necessary as first-line therapy for adult and pediatric individuals undergoing autologous peripheral blood progenitor cell collection and therapy.** **Note:** Nivestym (filgrastim-aafi) does not need preapproval for coverage. **Neupogen (filgrastim), Nypozi (filgrastim-txid), and Zarxio (filgrastim-sndz) may be considered medically necessary as second-line therapy for adult and pediatric individuals undergoing autologous peripheral blood progenitor cell collection and therapy when all the following are met:** • Documentation is provided that the individual has tried and failed Nivestym (filgrastim-aafi) **OR** • There is a contraindication to the use of Nivestym (filgrastim-aafi)
• **Neupogen (filgrastim)** • **Neulasta (pegfilgrastim)** • **Neulasta Onpro (pegfilgrastim)** • **Zarxio (filgrastim-sndz)** • **Ziextenzo (pegfilgrastim-bmez)**	**Neupogen (filgrastim), Neulasta (pegfilgrastim), Neulasta Onpro (pegfilgrastim), Zarxio (filgrastim-sndz), and Ziextenzo (pegfilgrastim-bmez) may be considered medically necessary as first-line therapy in adult and pediatric individuals acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).**
• **Neupogen (filgrastim)** • **Nivestym (filgrastim-aafi)** • **Nypozi (filgrastim-txid)** • **Releuko (filgrastim-ayow)** • **Zarxio (filgrastim-sndz)**	**Nivestym (filgrastim-aafi) may be considered medically necessary as first-line therapy to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.** **Note:** Nivestym (filgrastim-aafi) does not need preapproval for coverage.

Agent	Medical Necessity, Other Uses
	Neupogen (filgrastim), Nypozi (filgrastim-txid), Releuko (filgrastim-ayow), and Zarxio (filgrastim-sndz) may be considered medically necessary as second-line therapy to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric individuals with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia when all the following are met: • Documentation is provided that the individual has tried and failed Nivestym (filgrastim-aafi) **OR** • There is a contraindication to the use of Nivestym (filgrastim-aafi)
• **Fulphila (pegfilgrastim-jmdb)** • **Fylnetra (pegfilgrastim-pbbk)** • **Neulasta (pegfilgrastim)** • **Neulasta Onpro (pegfilgrastim)** • **Nyvepria (pegfilgrastim-apgf)** • **Stimufend (pegfilgrastim-fpgk)** • **Udenyca (pegfilgrastim-cbqv** • **Udenyca Onbody (pegfilgrastim-cbqv)** • **Ziextenzo (pegfilgrastim-bmez)**	**Fulphila (pegfilgrastim-jmdb), Udenyca (pegfilgrastim-cbqv), and Udenyca Onbody (pegfilgrastim-cbqv) may be considered medically necessary as first-line therapy when used in combination with chemotherapy regimens where pegfilgrastim was the only G-CSF product used in published clinical trials.** • When using Fulphila (pegfilgrastim-jmdb), Udenyca (pegfilgrastim-cbqv) and Udenyca Onbody (pegfilgrastim-cbqv) for this reason, the requesting provider should provide article citations supporting the request. **Fylnetra (pegfilgrastim-pbbk), Neulasta (pegfilgrastim), Neulasta Onpro (pegfilgrastim), Nyvepria (pegfilgrastim-apgf), Stimufend (pegfilgrastim-fpgk), and Ziextenzo (pegfilgrastim-bmez) 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:** • Documentation is provided that the individual has tried and failed Fulphila (pegfilgrastim-jmdb) AND Udenyca (pegfilgrastim-cbqv) or Udenyca Onbody (pegfilgrastim-cbqv)

Agent	Medical Necessity, Other Uses
	OR • Documentation is provided that the individual has a contraindication to the use of Fulphila (pegfilgrastim-jmdb) AND Udenyca (pegfilgrastim-cbqv) or Udenyca Onbody (pegfilgrastim-cbqv)

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **Any other uses of the following G-CSF products not addressed in this policy are considered investigational:** • Fulphila (pegfilgrastim-jmdb) • Fylnetra (pegfilgrastim-pbbk) • Granix (tbo-filgrastim) • Neulasta (pegfilgrastim) / Neulasta Onpro • Neupogen (filgrastim) • Nivestym (filgrastim-aafi) • Nypozi (filgrastim-txid) • Nyvepria (pegfilgrastim-apgf) • Releuko (filgrastim-ayow) • Rolvedon (eflapegrastim-xnst) • Ryzneuta (efbemalenograstim alfa-vuxw) • Stimufend (pegfilgrastim-fpgk) • Udenyca (pegfilgrastim-cbqv) • Udenyca Onbody (pegfilgrastim-cbqv) • Zarxio (Filgrastim-sndz) • Ziextenzo (pegfilgrastim-bmez)

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months.**

Length of Approval	
Approval	**Criteria**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual'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	
C9173	Injection, filgrastim-txid (nypozi), biosimilar, 1 microgram (new code effective 01/01/25)
J1442	Injection, filgrastim (G-CSF) (Neupogen), 1 microgram
J1449	Injection, eflapegrastim-xnst (Rolvedon), 0.1 mg
J2506	Injection, pegfilgrastim (Neulasta), excludes biosimilar, 0.5 mg
J3590	Unclassified biologics (Use to report Rolvedon)
J9361	Injection, efbemalenograstim alfa-vuxw, (Ryzneuta) 0.5 mg (new code effective 7/1/2024)
Q5101	Injection, filgrastim-sndz, biosimilar, (Zarxio), 1 microgram
Q5108	Injection, pegfilgrastim-jmdb (Fulphila), biosimilar,0.5 mg
Q5111	Injection, pegfilgrastim-cbqv, (Udenyca), biosimilar, 0.5 mg

Code	Description
Q5120	Injection, pegfilgrastim-bmez, (Ziextenzo), biosimilar, 0.5 mg
Q5122	Injection, pegfilgrastim-apgf, (Nyvepria), biosimilar, 0.5 mg
Q5125	Injection, filgrastim-ayow, biosimilar, (Releuko), 1 mcg
Q5127	Injection, Pegfilgrastim-fpgk (Stimufend), biosimilar, 0.5 mg
Q5130	Injection, Pegfilgrastim-pbbk (Fylnetra), biosimilar, 0.5 mg

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

For purposes of this policy, the following types of individuals are considered to be at risk of severe FN:

- Individuals that have experienced FN during a previous cycle of treatment with the current chemotherapy regimen

OR

- Individuals 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

- Individuals with bone marrow impairment

OR

- Individuals that have received 2 or more prior chemotherapy regimens or extensive radiation

OR

- Individuals 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).

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 deoxyribonucleic acid (DNA) technology using the bacterium strain Escherichia coli (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 US Food and Drug Administration (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 individuals with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia (FN) 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 G-CSF 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 G-CSF 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 individuals with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs in one of the following categories:

1. Cancer individuals receiving myelosuppressive chemotherapy

2. Individuals with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy
3. Cancer individuals receiving bone marrow transplantation
4. Individuals undergoing Peripheral Blood Progenitor Cell Collection and Therapy
5. Individuals with Severe Chronic Neutropenia
6. Individuals in these categories are associated with a significant incidence of severe FN.

Nypozi (filgrastim-txid)

Filgrastim-txid, a leukocyte growth factor, is a 175 amino acid human G-CSF manufactured by recombinant DNA technology. Filgrastim-txid is produced by E. coli bacteria into which has been inserted the human G-CSF gene. Filgrastim-txid 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 filgrastim-txid is produced in E. coli, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

Releuko (filgrastim-ayow)

Filgrastim-ayow, a leukocyte growth factor, is a 175 amino acid human G-CSF manufactured by recombinant DNA technology. Filgrastim-ayow is produced by E. coli bacteria into which has been inserted the human G-CSF gene. Filgrastim-ayow 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 filgrastim-ayow is produced in E coli, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell. Kanamycin, 50 mcg/mL is final concentration, is used during the fermentation step of the manufacturing process. Kanamycin is not detectable in the final product.

Zarxio (filgrastim-sndz)

A 175 amino acid human G-CSF manufactured by recombinant DNA technology. Zarxio (filgrastim-sndz) is produced by E. coli bacteria into which has been inserted the human G-CSF 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 individuals 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.

Fylnetra (pegfilgrastim-pbbk)

Fylnetra (pegfilgrastim-pbbk) is a biosimilar to Neulasta (pegfilgrastim). Pegfilgrastim-pbbk 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-pbbk, 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-pbbk is approximately 39 kD.

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 Onbody

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.

Stimufend (pegfilgrastim-fpgk)

Stimufend (pegfilgrastim-fpgk) is a biosimilar to Neulasta (pegfilgrastim). Pegfilgrastim-fpgk 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-fpgk, 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-fpgk is approximately 39 kD.

Rolvedon (eflapegrastim-xnst)

Eflapegrastim-xnst is a G-CSF produced by covalent coupling of a human G-CSF analog (18.6 kDa) and an Fc fragment of human immunoglobulin G4 (IgG4) (49.8 kDa), both derived from recombinant E. coli, via a single 3.4 kDa polyethylene glycol linker. The recombinant G-CSF domain in eflapegrastim-xnst is a variant of human G-CSF with two serine substitutions at positions 17 and 65, and no additional N-terminal methionine. Eflapegrastim-xnst has a molecular weight of approximately 72 kDa.

Ryzneuta (efbemalenograstim alfa-vuxw)

Efbemalenograstim alfa-vuxw, a leukocyte growth factor, is a 413 amino acid recombinant fusion protein consisting of human G-CSF, a 16 amino-acid linker, and the Fc portion of human IgG2. In solution, efbemalenograstim alfa-vuxw forms covalently-linked dimers (disulfide bonds between Fc moieties), resulting in an immunoglobulin-like structure. The dimer is a water-soluble, glycosylated protein with a molecular weight of approximately 93.4 kilodaltons (kDa), of which 89.5 kDa is attributed to amino acids (protein sequence) and the remainder is from

glycosylation. Efbemalenograstim alfa-vuxw is obtained from genetically-engineered strain of Chinese hamster ovary (CHO) cells grown in a serum-free medium.

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,Releuko, and then Nypozi. Fulphila is the first biosimilar pegfilgrastim product followed by Udenyca, Ziextenzo, Nyvepria, Fylnetra, and then Stimufend. 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					
Fylnetra	X					
Granix	X					
Neulasta	X					X
Neupogen	X	X	X	X	X	X
Nivestym	X	X	X	X	X	
Nypozi	X	X	X	X	X	X
Nyvepria	X					
Udenyca	X					
Releuko	X	X	X		X	
Rolvedon	X					
Ryzneuta	X					
Stimufend	X					
Zarxio	X	X	X	X	X	X
Ziextenzo	X					X

Contraindications

Fulphila, Fylnetra, Granix, Neulasta, Neulasta Onpro, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Stimufend, Udenyca, Udenyca Onbody, Zarxio and Ziextenzo are contraindicated in individuals with a history of serious allergic reactions to human G-CSFs such as pegfilgrastim or filgrastim products.

Rolvedon is contraindicated in individuals with a history of serious allergic reactions to human G-CSFs such as eflapegrastim, pegfilgrastim, or filgrastim products.

Ryzneuta is contraindicated in individuals with a history of serious allergic reactions to human G-CSFs such as efbemalenograstim alfa-vuxw, pegfilgrastim, or filgrastim products.

Benefit Application

Fulphila, Fylnetra, Granix, Neulasta, Neulasta Onpro, Neupogen, Nivestym, Nypozi, Nyvepria, Releuko, Rolvedon, Ryzneuta, Stimufend, Udenyca, Udenyca Onbody, Zarxio, and Ziextenzo may be managed under either the medical benefit (if administered by a provider) or pharmacy benefit (if administered by the individual 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 individuals with high-risk stage II, stage III, or stage IV breast cancer.

Neulasta (pegfilgrastim) has been shown to be 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 individuals compared to the placebo treated individuals.

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 individuals 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 individuals (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 granulocyte colony-stimulating factors (G-CSF) to mobilize stem cells.

The efficacy, safety, and tolerability of eflapegrastim compared to pegfilgrastim have been demonstrated in two nearly identical, moderate-to-good quality, multicenter, randomized, open-label, noninferiority (NI), Phase 3 trials (ADVANCE and RECOVER). A total of 660 individuals with early-stage breast cancer being treated with neoadjuvant or adjuvant

docetaxel/cyclophosphamide chemotherapy were randomized to eflapegrastim 13.2 mg (equivalent to 3.6 mg GCSF; n=334) or pegfilgrastim (equivalent to 6 mg GCSF; n=326) on day 2 following docetaxel/cyclophosphamide chemotherapy for each of 4 cycles. Safety assessments continued for 1 year following the last dose of study medication. The primary study endpoint was NI for duration of severe neutropenia (absolute neutrophil count [ANC] <0.5 x 109/L) in cycle 1, with a NI margin of <0.62 days.

In the ADVANCE trial, mean (standard deviation [SD]) duration of severe neutropenia in cycle 1 was 0.20 (0.503) days for eflapegrastim and 0.35 (0.683) days for pegfilgrastim, demonstrating NI for eflapegrastim vs. pegfilgrastim (95% CI of DSN change: [-0.264, -0.032]; *P* <0.0001. NI for eflapegrastim for duration of severe neutropenia was maintained across all 4 cycles.

In the RECOVER trial, mean (SD) duration of severe neutropenia in cycle 1 was 0.31 (0.69) days for eflapegrastim and 0.39 (0.95) days for pegfilgrastim, demonstrating NI for eflapegrastim vs. pegfilgrastim (95% CI of duration of severe neutropenia change: [-0.292, -0.129]; *P* <0.0001. The NI for eflapegrastim for duration of severe neutropenia was maintained across all 4 cycles.

Supporting the NI primary endpoint findings there was no significant differences between the treatments in all secondary endpoints (time to ANC recovery, depth of ANC nadir, incidence of febrile neutropenia at cycle 1, neutropenic complications [antibiotic use or hospitalization], and relative dose intensity) in both trials.

Safety

In clinical trials, the most common adverse events for filgrastim and pegfilgrastim 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 individuals with sickle cell disorders, and the potential for tumor growth stimulatory effects on malignant cells.

The safety profile for eflapegrastim appears similar to pegfilgrastim based on current clinical trial evidence. No leukocytosis, splenic rupture, or anaphylaxis was reported in either treatment group. Overall incidence of immunogenicity was similar in both groups and no impact on clinical efficacy or safety was observed. The most common adverse reactions (≥20%) for eflapegrastim listed in the prescribing information are fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia, and back pain.

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 individual 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 US Food and Drug Administration (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).

2021 Update

Reviewed prescribing information for all drugs listed in policy. No new evidence was identified that would change coverage criteria.

2022 Update

Reviewed prescribing information for all drugs listed in policy and researched product availability. Added Releuko (filgrastim-ayow), a biosimilar to Neupogen (filgrastim), to policy for the treatment of individuals receiving myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia. Compared to the other two biosimilar filgrastim products, Nivestym and Zarxio, Releuko is not FDA-approved to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. Added Fylnetra (pegfilgrastim-pbbk), a biosimilar to Neulasta (pegfilgrastim), to policy for the treatment of individuals receiving myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia.

2023 Update

Reviewed prescribing information for all drugs listed in policy. No new evidence was identified that would change coverage criteria.

2024 Update

Reviewed prescribing information for all drugs listed in policy. Added Ryzneuta (efbemalenograstim alfa-vuxw) and Udenyca Onbody (pegfilgrastim-cbqv) as non-preferred

treatments to the policy for the treatment of individuals receiving myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia. Updated coverage criteria for Neupogen (filgrastim), Nivestym (filgrastim-aafi), Releuko (filgrastim-ayow), and Zarxio (filgrastim-sndz) to include coverage for certain individuals with congenital neutropenia, cyclic neutropenia, and idiopathic neutropenia. Updated coverage criteria for Ziextenzo (pegfilgrastim-bmez) to include coverage for individuals acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). Added Nypozi (filgrastrim-txid) as a non-preferred treatment for all labeled indications. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

2025 Update

Reviewed prescribing information for all drugs listed in policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Moved Udenyca (pegfilgrastim-cbqv) and Udenyca Onbody (pegfilgrastim-cbqv) from second-line to first-line therapy for individuals less than 18 years of age and moved Nyvepria (pegfilgrastim-apgf) from first-line to second-line therapy for individuals less than 18 years of age. Moved Udenyca (pegfilgrastim-cbqv) and Udenyca Onbody (pegfilgrastim-cbqv) from third-line to second-line therapy for adults and moved Nyvepria (pegfilgrastim-apgf) from second-line to third-line therapy for adults. Updated coverage criteria for Zarxio (filgrastim-sndz) to include coverage for individuals acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

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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
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

Regimen	Acronym	FN (%)	Cancer
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 + Means + 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
Docetaxel + Cyclophosphamide	TC	21	Metastatic gastric cancer
Docetaxel + Cyclophosphamide + Fluorouracil	TCF	41	Metastatic gastric cancer
Antithymocyte globulin, rabbit/cyclosporine		> 20	Myelodysplastic
Decitabine		> 20	Myelodysplastic

Regimen	Acronym	FN (%)	Cancer
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 + Dexamethasone	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
Etoposide + Cisplatin		54	NSCLC
Cisplatin + Vinorelbine + Cetuximab		22	NSCLC
Vinorelbine + Ifosfamide + Gemcitabine	VIG	25	NSCLC
Topotecan		> 20	Ovarian
Docetaxel		33	Ovarian
Paclitaxel		22	Ovarian

Regimen	Acronym	FN (%)	Cancer
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 outlined 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.

Date	Comments
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.
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).

Date	Comments
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 1, 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.
12/01/21	Annual Review, approved November 18, 2021. No changes to policy statements. Added HCPCS code J2506.
07/01/22	Annual Review, approved June 27, 2022. Added coverage for Releuko (filgrastim-ayow) and Fylnetra (pegfilgrastim-pbbk) for the treatment of patients receiving myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia. Added HCPCS codes C9096 and J3590.
10/01/22	Coding update. Added HCPCS code Q5125.
11/01/22	Interim Review, approved October 11, 2022. Added coverage for Rolvedon (eflapegrastim-xnst) for the treatment of adults receiving myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia. Added coverage for Stimufend (pegfilgrastim-fpgk) for the treatment of patients receiving myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia. Added Rolvedon and Stimufend to HCPC code J3590. Changed the wording from "patient" to "individual" throughout the policy for standardization.
01/01/23	Coding update. Removed termed HCPC code J2505 and new code date on HCPC code J2506. Repositioned drug name Neulasta within HCPC code J2506 description.
04/01/23	Coding update. Updated the coding description for HCPC codes Q5108, Q5111, Q5120, and Q5122. Added new HCPC codes Q5127 and Q5130. Removed Fylnetra and Stimufend name from HCPC code J3590.
09/01/23	Interim Review, approved August 23, 2023. Changed preferred and non-preferred biosimilar pegfilgrastim products. Moved Fulphila and Nyvepria from second-line to first-line therapy for individuals less than 18 years of age and moved Udenyca and Ziextenzo from first-line to second-line therapy for individuals less than 18 years of age. Moved Fulphila and Nyvepria from third-line to second-line therapy for adults and moved Udenyca and Ziextenzo from second-line to third-line therapy for adults. These policy updates are effective for dates of service on or after January 1, 2024, following a 90-day provider notification.

Date	Comments
12/01/23	Annual Review, approved November 20, 2023. No changes to policy statements.
02/01/24	Annual Review, approved January 9, 2024. Added Ryzneuta (efbemalenograstim alfa-vuxw) and Udenyca Onbody (pegfilgrastim-cbqv) as non-preferred treatments to the policy for the treatment of individuals receiving myelosuppressive anti-cancer regimens at risk of severe febrile neutropenia. Added Ryzneuta to HCPC code J3590.
03/01/24	Interim Review, approved February 13, 2024. Updated coverage criteria for Neupogen (filgrastim), Nivestym (filgrastim-aafi), Releuko (filgrastim-ayow), and Zarxio (filgrastim-sndz) to include coverage for certain individuals with congenital neutropenia, cyclic neutropenia, and idiopathic neutropenia. Added HCPCS code J1449.
07/01/24	Coding update. Added new HCPCS code J9361 effective 7/1/2024. Removed drug name Ryzneuta from unlisted HCPCS code, J3590.
12/01/24	Interim Review, approved November 12, 2024. Updated coverage criteria for Ziextenzo (pegfilgrastim-bmez) to include coverage for patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). Added Nypozi (filgrastrim-txid) as a non-preferred treatment for all labeled indications.
01/01/25	Interim Review, approved December 23, 2024. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Added new HCPCS code C9173.
03/01/25	Annual Review, approved February 11, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Updated coverage criteria for Zarxio (filgrastim-sndz) to include coverage for individuals acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). The following policy changes are effective July 1, 2025, following a 90-day provider notification. Moved Udenyca (pegfilgrastim-cbqv) and Udenyca Onbody (pegfilgrastim-cbqv) from second-line to first-line therapy for individuals less than 18 years of age and moved Nyvepria (pegfilgrastim-apgf) from first-line to second-line therapy for individuals less than 18 years of age. Moved Udenyca (pegfilgrastim-cbqv) and Udenyca Onbody (pegfilgrastim-cbqv) from third-line to second-line therapy for adults and moved Nyvepria (pegfilgrastim-apgf) from second-line to third-line therapy for adults.

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.