DRUG DETERMINATION POLICY

Title: DDP-15 G-CSF Agents

Effective Date: 12/15/2020

Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

1.0 Policy:

This policy describes the determination process for coverage of specific drugs that require prior approval.

This policy does not guarantee or approve Benefits. Coverage depends on the specific Benefit plan. Pharmacy Benefit Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

2.0 Background or Purpose:

Granulocyte colony-stimulating factor (G-CSF) agents are specialty drugs indicated for a number of diagnoses and are associated with significant toxicity. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and mitigation of toxicity, if possible.

3.0 Clinical Determination Guidelines:

Document the following with chart notes:

A. Filgrastim subcutaneous (Nivestym SQ).
    1. Status: preferred agent (brand Nivestym).
    2. Quantity limits:
        a. Covered without prior authorization: ten syringes per 24 days.
        b. Prior authorization required: greater than ten syringes per 24 days.
    3. Excluded filgrastim products: Neupogen, Zarxio, Granix.
        a. All preferred products contraindicated, inadequate response or had significant adverse effects.

B. Pegfilgrastim subcutaneous (brand-names: Fulphila, Udenyca, Ziextenzo SQ).
    1. Status: non-preferred agent.
    2. Diagnosis and severity [must meet one listed below]:

a. Prevention of chemotherapy-induced neutropenia: to decrease the incidence of infections in patients with non-myeloid malignancies receiving myelosupressive cancer chemotherapy associated with significant incidence of febrile neutropenia.

b. Hematopoietic radiation injury syndrome, acute: to increase survival in patients acutely exposed to myelosuppressive doses of radiation [must meet all listed below]:

- Radiation exposure: at least two Gray.
- Absolute lymphocyte count: significant decrease.
- Neutropenia: anticipated to be less than 500/mm^3 for at least seven days.

3. Non-preferred pegfilgrastim approval [must meet one listed below]:

a. Failure of filgrastim: required greater ten days of daily filgrastim therapy to obtain acceptable absolute neutrophil count (ANC).

b. Significant adverse effects or administration issues with filgrastim.

c. Significant physical limitation that limits ability to perform daily injections with no other individual able to perform injection.

d. Patient at high risk for febrile neutropenia (see Appendix II).

4. Excluded products: Neulasta, Neulasta Onpro.

a. All preferred products contraindicated, inadequate response or had significant adverse effects.

5. Dosage regimen.

a. Adult:

- Prevention of chemotherapy-induced neutropenia: 6mg subcutaneous (SQ) once per chemotherapy cycle, beginning at least 24 hours after completion of chemotherapy.
- Hematopoietic radiation injury, acute: 6mg SC weekly for two doses.

b. Pediatric:

- Prevention of chemotherapy-induced neutropenia: once dose subcutaneous (SC) once per chemotherapy cycle, beginning at least 24 hours after completion of chemotherapy.
- Hematopoietic radiation injury, acute: subcutaneous (SC) weekly for two doses.
- Dose by weight:

Weight (Kg)	Route	Dose	Volume
Below 10	Subcutaneous (SQ)	0.1 mg/kg	0.01 mL/kg
10 to 20	SQ	1.5 mg	0.15 ml
21 to 30	SQ	2.5 mg	0.25 ml

Weight (Kg)	Route	Dose	Volume
31 to below 45	SQ	4 mg	0.4 ml
Over 45	SQ	6mg	0.6 ml

C. Approval [must meet both below]:

1. Duration: six months or less depending on the number of cycles.

2. Billing: through the outpatient prescription drug benefit only.

D. Appropriate medication use [must meet one listed below]:

1. FDA approval status [must meet one listed below]:

   a. FDA approved: product, indication, and/or dosage regimen.

   b. Off-label use: at least two supporting studies from major peer-reviewed medical journals that support the off-label use as safe and effective.

2. Place in therapy: sequence of therapy supported by national or international accepted guidelines and/or studies (e.g., oncologic, infectious conditions).

4.0 Coding:

Filgrastim and pegfilgrastim products are covered under the outpatient prescription drug benefit only.

5.0 Unique Configuration/Prior Approval/Coverage Details:

None.

6.0 References, Citations & Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; filgrastim accessed October 2020.
2. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; pegfilgrastim, accessed October, 2020.
3. Amgen https://www.neulastahcp.com/febrile-neutropenia/?febrile+neutropenia+informationUNB_HCP_Awareness_General_PHM_05.2020FN+General_PHM&utm_source=bing&utm_medium=cpc&utm_campaign=UNB_HCP_Awareness_General_PHM_05.2020&utm_term=febrile%20neutropenia%20information&utm_content=FN%20General_PHM&gclid=CL3u76_-yuwCFZqPxQId6EwCuQ&gclsrc=ds. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology accessed October 20 (NCCN Guidelines®) for Myeloid Growth Factors V.2.2018. ©National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed August 3, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. ©NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

7.0 Appendices:

See page 5-6.

8.0 Revision History:

Original Effective Date: 12/14/2005

Next Review Date: 03/24/2021

Revision Date	Reason for Revision
March 2019	Transfer to new format
April 2019	Presented and approved at P & T Workgroup
12/19	Off cycle review; addition of biosimilars; change to consistent verbiage, replace abbreviations.
3/20	Annual review; revised indication, added adult and pediatric dosage regimen
10/20	Off cycle review, clarified preferred agents, non-preferred criteria & criteria instructions; added filgrastim to Monitoring and Patient safety appendix, added D. appropriate medication use, approved at 10/28/20 P&T

Appendix I: Monitoring & Patient Safety - Adverse Reactions and Monitoring

Drug	Adverse Reactions	Monitoring	REMS
Pegfilgrastim (Neulasta, Fulphila, Udenyca, Ziextenzo)	• Musculoskeletal: ostealgia (31%) • Pregnancy Category: C	• Gastro-Intestinal (GI): abdominal pain • Hematology: monitor for sickle cell crisis, splenomegaly • Hypersensitivity • Musculoskeletal: shoulder pain • Pregnancy: adverse event in animal studies • Renal: glomerulonephritis • Respiratory: pulmonary infiltrates, respiratory distress • Myelosuppressive chemotherapy: complete blood count (CBC) with difference and platelets prior to and as needed • Hematopoietic radiation injury syndrome: CBC at baseline, established absorbed radiation dose	None needed
Filgrastim (Neupogen, Nivestym , Granix, Zarsio)	• Cardiovascular: chest pain (5-13% • Central nervous system: fatigue (20%) dizziness (14%), pain (12%) • Dermatologic: skin rash (2%-14%) • Gastrointestinal: nausea (43%) • Hematologic & oncologic: thrombocytopenia (5%-38%), splenomegaly (≥5%; severe chronic neutropenia: 30%) • Hepatic: increased serum alkaline phosphatase (6%-11%) • Neuromuscular & skeletal: ostealgia (11%-30%), back pain (2%-15%) • Respiratory: epistaxis (≥5%), cough (14%), dyspnea (13%) • Miscellaneous: fever (8%-48%)		

Appendix II Risk Assessment for chemotherapy-induced Neutropenia

According to the American Society of Clinical Oncology (ASCO) and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Evaluate the risk of FN and administer primary CSF prophylaxis in first and subsequent cycles for patients at > 20% risk[1,2]

When assessing risk, evaluate both chemotherapy regimen and patient risk factors[2]

Select chemotherapy regimens associated with a HIGH RISK OF FN
Breast cancer
• TAC (docetaxel + doxorubicin + cyclophosphamide) Q3W[2,3,*] • TC (docetaxel + cyclophosphamide) Q3W[2,4,*] • TCH*± P† (docetaxel + carboplatin + trastuzumab with or without pertuzumab)[2,5,6]
Non-Hodgkin's lymphoma
• BR (bendamustine + rituximab)[7,†] • CHOP*,† ± R† (cyclophosphamide + doxorubicin + vincristine + prednisolone with or without rituximab) Q3W[2,8,9]
Non-small cell lung cancer
• Carboplatin + paclitaxel Q3W[10,‡]
Small cell lung cancer
• Topotecan[2,*]

Select chemotherapy regimens associated with an INTERMEDIATE RISK OF FN
Breast cancer
• AC (doxorubicin + cyclophosphamide) + sequential docetaxel[11,†]
Non-small cell lung cancer
• Cisplatin + etoposide[2,*] • Cisplatin + docetaxel[2,12,*] • Carboplatin + docetaxel[13,†]
Prostate cancer
• Cabazitaxel[2,*] • Docetaxel + prednisone[14,†]
Small cell lung cancer
• Carboplatin + etoposide[2,*]

Even one of these select risk factors can increase risk:[2,§]

- Baseline cytopenias[16,17]
- Poor performance status (ECOG ≥ 2)[18]
- Age ≥ 65 years[17]
- COPD[19,**]
- Chronic immunosuppression in the post-transplant setting, including organ transplant[16]
- Liver disease[20]
- Renal disease[17]
- Cardiovascular disease[17,**]
- Diabetes[21,**]
- Prior chemotherapy[22]
- Prior radiotherapy[16]
- Poor nutritional status[23,**]
- Decreased serum albumin[23,**]
- Open wounds/recent surgery[24]
- Active infections[25,**]
- HIV[20]
- Metastatic[18,**]
- Elevated lactate dehydrogenase[23,**]

§The patient risk factors included here have been identified through published literature and clinical guidelines. This list is not exhaustive. There may be other risk factors that apply based on available research and the clinical judgment of the treating physicians. These risk factors in addition to high or intermediate risk chemotherapy regimens can increase the risk of infection.

**Risk factors not listed by the NCCN.

COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus.