Reference number(s)
4237-A

STANDARD MEDICARE PART B MANAGEMENT

NEULASTA (pegfilgrastim)
FULPHILA (pegfilgrastim-jmdb)
FYLNETRA (pegfilgrastim-pbbk)
NYVEPRIA (pegfilgrastim- apgf)
STIMUFEND (pegfilgrastim-fpgk)
UDENYCA (pegfilgrastim-cbqv)
ZIEXTENZO (pegfilgrastim-bmez)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

Neulasta

1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
   Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
2. Hematopoietic Subsyndrome of Acute Radiation Syndrome
   Neulasta is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

Fulphila

Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Udenyca

Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Ziextenzo

Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Nyvepria

Indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with

non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Fylnetra
Patients with Cancer Receiving Myelosuppressive Chemotherapy
Fylnetra is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Stimufend
Patients with Cancer Receiving Myelosuppressive Chemotherapy
Stimufend is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

B. Compendial Uses
1. Stem cell transplantation-related indications
2. Prophylaxis for chemotherapy-induced febrile neutropenia in patients with solid tumors
3. Hematopoietic Subsyndrome of Acute Radiation Syndrome
4. Hairy cell leukemia, neutropenic fever

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
Primary Prophylaxis of Febrile Neutropenia
Documentation of the member's diagnosis and chemotherapeutic regimen.

III. CRITERIA FOR INITIAL APPROVAL

A. Prevention of neutropenia in cancer patients receiving myelosuppressive chemotherapy
Authorization of 6 months may be granted for prevention of febrile neutropenia for members with solid tumors or non-myeloid malignancies when the requested medication will not be administered with weekly chemotherapy regimens and the member will not be receiving chemotherapy and radiation therapy at the same time.

B. **Other indications**
Authorization of 6 months may be granted for members with any of the following indications:
1. Stem cell transplantation-related indications
2. Hematopoietic subsyndrome of acute radiation syndrome
3. Hairy cell leukemia with neutropenic fever following chemotherapy

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Neulasta, Fulphila, Fylnetra, Nyvepria, Stimufend, Udenyca, and Ziextenzo.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Hematopoietic growth factors
4. NCCN Guideline: Hematopoietic cell transplantation
5. NCCN Guideline: Hairy cell leukemia

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Neulasta and its biosimilars are covered in addition to the following:

A. Stem cell transplantation-related indications
B. Prophylaxis for chemotherapy-induced neutropenia in patients with solid tumors
C. Hairy cell leukemia, neutropenic fever

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer’s prescribing information.

Support for using pegfilgrastim in mobilization of peripheral blood progenitor cells can be found in a study of patients with non-Hodgkin lymphoma by Russel et al. Patients with non-Hodgkin's lymphoma received one cycle of mobilizing chemotherapy (ifosfamide, carboplatin and etoposide, ICE). Twenty-four hours later they were randomized, double-blind, to receive a single dose of pegfilgrastim 6 mg or 12 mg, or filgrastim 5 mg/kg/day (until the end of leukapheresis). Following leukapheresis (collection phase), patients rested or received one or two 'salvage' cycles of ICE. High-dose BEAM chemotherapy was then given before peripheral blood progenitor cell transplantation. The primary end-point was the patients' mean yield of CD34(+) cells/kg during the collection phase. Ninety patients were randomized and received a study drug; 63% completed the collection phase. The patients' mean (95% CI) CD34(+) cell harvest per leukapheresis was 0.8 (0.5-1.4), 0.8 (0.5-1.6) and 1.2 (0.7-2.0)x10(6) cells/kg for the pegfilgrastim 6 mg, pegfilgrastim 12 mg and filgrastim groups, respectively. Twenty (69%), 17 (59%) and 23 (72%) patients in these three groups achieved the targeted minimum harvest (>/=2 x 10(6) cells/kg). The mean total harvests were 1.7, 1.4 and 2.2 x 10(6) cells/kg, respectively. Post-transplantation, the median days to absolute neutrophil count recovery (>/=0.5 x 10(9)/L) were 12, 11, and 11, respectively. Pegfilgrastim and filgrastim were generally well tolerated.

In a phase 2 study by Fruehauf et al, a single dose of pegfilgrastim 12 mg demonstrated favorable CD34+ cell yields when administered following myeloablative chemotherapy for the mobilization of peripheral blood progenitor cells (PBPC) in patients with multiple myeloma (MM). Patients aged 18 to 65 years (median age, 57 years; range, 40 to 65 years) with stage 2 or 3 MM who were candidates for an autologous transplant were

eligible for study enrollment. Most patients had previously received induction therapy with VAD (vincristine, doxorubicin, dexamethasone). Following myeloablative chemotherapy with CAD (cyclophosphamide, doxorubicin, dexamethasone), patients received a single dose of subcutaneous pegfilgrastim 12 mg (n=26) on day 5, approximately 24 hours after chemotherapy completion. In patients with a CD34+ cell count of 20 x 10(6) cells/L or greater (at day 10 or greater), leukapheresis was started between days 15 to 20 and continued until a CD34+ cell count fell to 5 x 10(6)/L or less or a target CD34+ cell harvest of 7.5 x 10(6)/kg was achieved. In patients with a CD34+ cell count between 5 and 20 x 10(6) cells/L (at day 13 or greater) and a platelet count of 30 x 10(9)/L, leukapheresis was continued until the target harvest of 7.5 x 10(6)/kg was achieved. Additional treatment with filgrastim 10 mcg/kg was given if the CD34+ cell count fell by greater than 25% per day starting from day 16 without reaching 20 x 10(6) cells/L. The transplant phase consisted of high-dose melphalan followed by PBPC transfusion. Patients were compared with historical control patients from the same center who received filgrastim (n=52; median age, 60 years; range, 31 to 70 years) matched (1:2) for prior therapy, disease stage, and induction therapy response before mobilization. A CD34+ cell target yield of 7.5 x 10(6) cells/kg or greater (primary endpoint) was achieved in 23 patients (88%; 95% confidence interval, 70% to 98%) who received pegfilgrastim and 41 patients (79%) who received filgrastim (median number of apheresis procedures to target CD34+ cell yield: pegfilgrastim, 2 (range, 1 to 4); filgrastim, 2 (range, 1 to 6)). Three patients who received pegfilgrastim required additional treatment with filgrastim to achieve the target CD34+ cell yield, and all 26 patients received a transplant. The median total CD34+ cell harvests were 9.7 X 10(6) cells/kg (range, 4.9 to 40.5 x 10(6) cells/kg) and 9.95 x 10(6) cells/kg (range, 2.6 to 99.9 X 10(6) cells/kg) for the pegfilgrastim and filgrastim groups, respectively; additionally, the median CD34+ cells per leukapheresis were 4.4 x 10(6) cells/kg (range, 0.9 to 40.5 x 10(6) cells/kg) and 3.4 x 10(6) cells/kg (range, 0.1 to 63.6 x 10(6) cells/kg), respectively. Hematologic recovery following transplant was similar in the pegfilgrastim and filgrastim groups for the median time to leucocyte count of 1 x 10(9)/L or greater (14 days (range, 10 to 21 days) and 14 days (range, 8 to 24 days), respectively) and median time to platelets of 20 x 10(9)/L or greater (11 days (range, 0 to 15 days) and 11 days (range, 0 to 16 days). Adverse events reported with pegfilgrastim use were grade 1 thoracic pain (n=1) and nausea (n=1).

Support for using pegfilgrastim in hematopoietic cell mobilization can be found in the National Comprehensive Cancer Network's guideline for hematopoietic cell transplantation. The NCCN Guideline for hematopoietic cell transplantation supports the use of pegfilgrastim as treatment for hematopoietic cell mobilization for autologous donors in combination with plerixafor.

Support for using pegfilgrastim for neutropenic fever in a patient being treated for hairy cell leukemia can be found in the National Comprehensive Cancer Network's guideline for hairy cell leukemia. The NCCN Guideline for hairy cell leukemia supports using neutrophil growth factors for patients with neutropenic fever following systemic therapy.

Support for hematopoietic acute radiation syndrome can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors in addition to the prescribing information for Neulasta. The NCCN Guideline for hematopoietic growth factors supports the use of pegfilgrastim in patients with radiation-induced myelosuppression following a radiologic/nuclear incident.

VII. REFERENCES

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