NEW DRUG APPROVAL

Brand Name	Fylnetra®
Generic Name	pegfilgrastim-pbbk
Drug Manufacturer	Kashiv BioSciences, LLC

New Drug Approval

FDA Approval Date: May 26, 2022

Review Designation: N/A

Review Type: Biologic License Application (BLA): 761084

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Febrile neutropenia (FN) is a serious complication of cancer chemotherapy that can lead to delays in treatment and necessary dose reductions of chemotherapy, which compromise treatment efficacy. Approximately 1% of patients with cancer receiving chemotherapy develop Febrile neutropenia, which contributes to morbidity and mortality, and imposes substantial burdens on healthcare resource use for management of this affected population.

Neutropenia is characterized by a reduction in neutrophils below normal counts, usually occurring within 7 to 12 days following cancer chemotherapy. It is diagnosed with a blood test that confirms an absolute neutrophil count (ANC) of less than 500 cells per microliter following cytotoxic chemotherapy, or by an ANC expected to decrease to less than 500 cells per microliter within 48 hours. Due to reduced levels of neutrophils in circulation, patients with neutropenia may have an impaired ability to fight infections. Hence, even a minor infection for patients with neutropenia may become very serious. It is crucial to monitor patients for signs and symptoms of infection, which may present as fever, chills, or sweats.

The specific frequency of agranulocytosis is unknown; It is estimated to be 1.0 to 3.4 cases per million people per year. Neutropenia was particularly associated with HIV infection, acute leukemias, and myelodysplastic syndromes. Drug-induced neutropenia has an incidence of one case per million persons per year. About 50% of patients with febrile neutropenia will develop an infection, of which 20% with profound neutropenia will observe bacteremia.

Efficacy

Patients with Cancer Receiving Myelosuppressive Chemotherapy:
Pegfilgrastim was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m2 and docetaxel 75 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of pegfilgrastim. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (ANC < 0.5 x 10^9 /L) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. Based on the correlation between the duration of severe neutropenia and the incidence of febrile neutropenia found in studies with filgrastim, duration of severe neutropenia was chosen as the primary endpoint in both studies, and the efficacy of pegfilgrastim was demonstrated by establishing comparability to filgrastim-treated patients in the mean days of severe neutropenia.

In Study 1, 157 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (6 mg) on day 2 of each chemotherapy cycle or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.

Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of pegfilgrastim-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the pegfilgrastim arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI - 0.2, 0.6)] and in Study 2 were 1.7 days in the pegfilgrastim arm compared to 1.6 days in the filgrastim arm [difference in means 0.1 (95% CI - 0.2, 0.4)].

A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.

Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m^2 administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature ≥ 38.2°C and ANC ≤ 0.5 x 10^9 /L) was lower for pegfilgrastim-treated patients as compared to placebo-treated patients (1% versus 17%, respectively, $p < 0.001$). The incidence of hospitalizations (1% versus 14%) and IV antiinfective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the pegfilgrastim-treated patients compared to the placebo-treated patients. Study 4 was a multicenter, randomized, open-label study to evaluate the efficacy, safety, and pharmacokinetics of pegfilgrastim in pediatric and young adult patients with sarcoma. Patients with sarcoma receiving chemotherapy age 0 to 21 years were eligible. Patients were randomized to receive subcutaneous pegfilgrastim as a single dose of 100 mcg/kg (n = 37) or subcutaneous filgrastim at a dose 5 mcg/kg/day (n = 6) following myelosuppressive chemotherapy. Recovery of neutrophil counts was similar in the pegfilgrastim and filgrastim groups. The most common adverse reaction reported was bone pain.

Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity.

WARNINGS & PRECAUTIONS

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Fylnetra® in patients with ARDS.
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Fylnetra® in patients with serious allergic reactions.
- Fatal sickle cell crises: Discontinue Fylnetra® if sickle cell crisis occurs.
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Fylnetra® if causality is likely. Thrombocytopenia: Monitor platelet counts.

- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using Fylnetra® in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML.

CONTRAINDICATIONS

Fylnetra® is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products. Reactions have included anaphylaxis.

Clinical Pharmacology

MECHANISMS OF ACTION

Pegfilgrastim products are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

Dose & Administration

ADULTS

Patients with cancer receiving myelosuppressive chemotherapy:

- 6 mg administered subcutaneously once per chemotherapy cycle.
- Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

PEDIATRICS

Table 2. Dosing of Fylnetra® for pediatric patients weighing less than 45 kg

Body Weight	Fylnetra® Dose	Volume to Administer
Less than 10 kg*	See below*	See below*
10 to 20 kg	1.5 mg	0.15 mL
21 to 30 kg	2.5 mg	0.25 mL
31 to 44 kg	4 mg	0.4 mL

*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Fylnetra®.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only.