NEW DRUG APPROVAL

Brand Name	Stimufend®
Generic Name	pegfilgrastim-fpgk
Drug Manufacturer	Fresenius Kabi USA, LLC

New Drug Approval

FDA Approval Date: September 01, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA): 761173

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Febrile neutropenia (FN) is characterized by a decrease in neutrophils number to values below 500 cells/ mm^3 and an occurrence of fever higher or similar to 38.3ºC. It commonly occurs in cancer patients as a result of chemotherapy regimens. Chemotherapy destroys carcinogenic cells but also attacks in many cases some normal cells including essential elements of the immune system. Fever is one of the characteristic symptoms of febrile neutropenia and is usually associated with the presence of an infection caused by various microorganisms. Bacteria, including Gram-positive isolates (currently dominating) and Gram-negative species (Dominant in the 1970s), are usually reported as the main microorganisms responsible for febrile neutropenia and cause complicated infections leading to death. Other types of microorganisms such as fungi and viruses are also associated with the condition.

Epidemiology: The epidemiology of febrile neutropenia is variable according to a multitude of factors such as the type of cancer, the age, and sex of the patient, the type and cycle of treatment. It has been reported that 50% of deaths in patients receiving chemotherapy for solid tumours is attributable to febrile neutropenia. In patients being administrated chemotherapy for acute leukemia, febrile neutropenia represents 50% to 75% of deaths. The rapid administration of antibiotics has triggered a response rate of up to 60% to 70% and reduced the mortality to 10%. In the USA, a mortality rate associated with grade 3 and 4 neutropenia ranging from 3.4 % to 10.5% with an overall mortality ranging from 6.8% to 9.5% was reported. In patients suffering of solid tumors and some hematological malignancies, the overall mortality rates are 5% and 11% respectively. This increases to 15% in patients with confirmed bacteraemia related to Gram-negative bacteria, whereas Gram-positive bacteraemia accounts for 5%. The group of patients which is at a higher risk of febrile neutropenia, and which exhibits the worst morbidity and mortality rates is constituted by the elderly patients.

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/m^2 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

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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 anti-infective 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.

Safety: The most common adverse reaction reported was bone pain and pain in extremity.

Safety

ADVERSE EVENTS

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity.

The following adverse reaction data in Table 1 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m2 every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg pegfilgrastim (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other.

Table 1. Adverse Reactions with ≥ 5% Higher Incidence in pegfilgrastim Patients Compared to Placebo in Study 3

Body System Adverse Reaction	Placebo (N = 461)	pegfilgrastim 6 mg subcutaneous on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		

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Bone pain	26%	31%
Pain in extremity	4%	9%

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving pegfilgrastim. No complications attributable to leukocytosis were reported in clinical studies.

WARNINGS & PRECAUTIONS

Splenic Rupture: It includes fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Stimufend®.

Acute Respiratory Distress Syndrome (ARDS): It can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Stimufend® for ARDS. Discontinue Stimufend® in patients with ARDS.

Serious Allergic Reactions: It includes anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Stimufend® in patients with serious allergic reactions. Do not administer Stimufend® to patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products.

Use in Patients with Sickle Cell Disorders: Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue Stimufend® if sickle cell crisis occurs.

Glomerulonephritis: It has occurred in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose-reduction or discontinuation of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose reduction or interruption of Stimufend®.

Leukocytosis: White blood cell (WBC) counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of complete blood count (CBC) during Stimufend® therapy is recommended.

Thrombocytopenia: It has been reported in patients receiving pegfilgrastim products. Monitor platelet counts.

Capillary Leak Syndrome: It has been reported after G-CSF administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Potential for Tumor Growth Stimulatory Effects on Malignant Cells: The granulocyte colony-stimulating factor (G-CSF) receptor through which pegfilgrastim products and filgrastim products act has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) in Patients with Breast and Lung Cancer: MDS and AML have been associated with the use of pegfilgrastim products in conjunction with chemotherapy and/or radiotherapy in patients with breast and lung cancer. Monitor patients for signs and symptoms of MDS/AML in these settings.

Aortitis: It has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain,

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malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop.

Nuclear Imaging: Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

CONTRAINDICATIONS

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as 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

6 mg single subcutaneous injection administered once per chemotherapy cycle.

PEDIATRICS

Table 2. Dosing of Stimufend® for Pediatric Patients Weighing Less Than 45 kg

Body Weight	Stimufend® Dose	Volume to Administer
Less than 10 kg*	**See below***	**See below***
10 - 20 kg	1.5 mg	0.15 mL
21 - 30 kg	2.5 mg	0.25 mL
31 - 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 Stimufend®.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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

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