NEW DRUG APPROVAL

Brand Name	Rolvedon™
Generic Name	eflapegrastim-xnst
Drug Manufacturer	Spectrum Pharmaceuticals, Inc.

New Drug Approval

FDA approval date: September 09, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA): 761148

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Neutropenia and its complications, including febrile neutropenia and infection, remain major toxicities associated with myelosuppressive systemic cancer chemotherapy.

Epidemiology: In a nationwide prospective cohort study, first-cycle febrile neutropenia occurred in 6% of adults with solid tumors being treated with myelosuppressive chemotherapy. Among patients with metastatic solid tumors, incidence of febrile neutropenia during myelosuppressive chemotherapy ranged from 13% to 21% in a large retrospective study.

Efficacy

The efficacy of Rolvedon™ to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs was evaluated in two 1:1 randomized, open-label, active-controlled non-inferiority studies of similar design (Study 1 [NCT02643420] and Study 2 [NCT02953340]) that enrolled a total of 643 patients with early-stage breast cancer. Docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 (TC) were administered intravenously every 21 days (on Day 1 of each cycle) for up to 4 cycles. A fixed dose of Rolvedon™ 13.2 mg/0.6 mL or pegfilgrastim (6 mg/0.6 mL) was administered subcutaneously on Day 2 of each cycle after TC chemotherapy.

The median age of patients enrolled in the two randomized studies was 60 years (Range: 24 to 88), the majority of patients were female (>99%), 77% were White and 12% were Black or African American.

Study 1 enrolled 406 patients; 196 patients to the Rolvedon™ arm and 210 patients to the pegfilgrastim arm. Study 2 enrolled 237 patients; 118 patients to the Rolvedon™ arm and 119 patients to the pegfilgrastim arm. Efficacy for both trials was based on the duration of severe neutropenia (DSN) in Cycle 1.

Efficacy results are shown in Table 1. In both studies, Rolvedon™ was non-inferior to pegfilgrastim. The distributions of the severe neutropenia events in percentage from Cycle 1 for Study 1 and Study 2 are presented in Figure 1

Table 1. Duration of Severe Neutropenia (DSN) in Cycle 1 (Study 1 and Study 2)

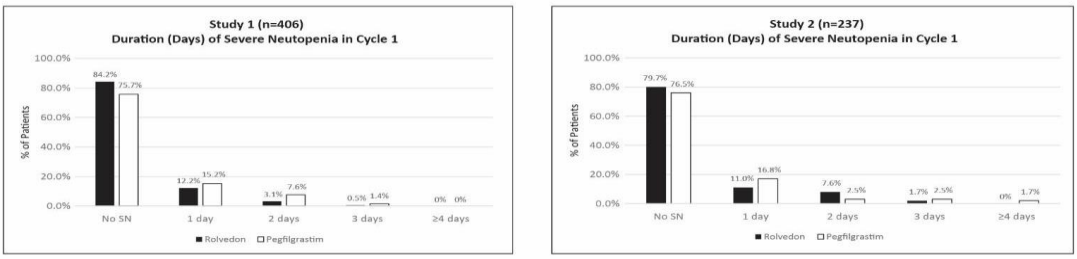
	Study 1		Study 2	
	Rolvedon™ (n=196)	**Pegfilgrastim (n=210)**	**Rolvedon™ (n=118)**	**Pegfilgrastim (n=119)**

Mean DSN (SD) (Days)	0.20 (0.503)	0.35 (0.683)	0.31 (0.688)	0.39 (0.949)
Median DSN (Range) (Days)	0 (0, 3)	0 (0, 3)	0 (0, 3)	0 (0, 7)
Difference in DSN (Days)	-0.148		-0.073	
*95% Confidence Interval[a]	-0.265, -0.033		-0.292, 0.129	

[a] Confidence intervals were obtained using 2.5 percentile and 97.5 percentile of the 100,000 bootstrap samples with treatment as stratification factor.

*The non-inferiority of Rolvedon™ to pegfilgrastim was to be declared if the upper bound of 95% CI of the difference in mean DSN between the treatment arms was <0.62 days.

Figure 1: Duration of Severe Neutropenia (DSN) by Day in Cycle 1 (Study 1 and Study 2)



Safety: The most common adverse reactions (≥20%) are fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia, and back pain.

Safety

ADVERSE EVENTS

Patients with early-stage breast cancer received Rolvedon™ 13.2 mg by subcutaneous injection (n=314) or pegfilgrastim 6 mg by subcutaneous injection (n=326) on Day 2 of each cycle after docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 (TC) chemotherapy. Among patients receiving Rolvedon™, a total of 272 patients received four 21-day treatment cycles. The most common adverse reactions (≥20%) were fatigue, nausea, diarrhea, bone pain, headache, pyrexia, anemia, rash, myalgia, arthralgia, and back pain. Table 2 summarizes the adverse reactions.

Table 2. Common Adverse Reactions with a Frequency of ≥ 10% Through Week 14 in Patients with Early-Stage Breast Cancer in Study 1 and Study 2

Adverse Reaction	Rolvedon™ (N = 314) %	Pegfilgrastim** (N=326) %
Fatigue*	181 (58%)	192 (59%)

Nausea	162 (52%)	166 (51%)
Diarrhea	125 (40%)	126 (39%)
Bone pain	119 (38%)	121 (37%)
Headache*	92 (29%)	90 (28%)
Pyrexia*	87 (28%)	84 (26%)
Anemia*	77 (25%)	52 (16%)
Rash*	77 (25%)	99 (30%)
Myalgia	69 (22%)	49 (15%)
Arthralgia	66 (21%)	48 (15%)
Back pain*	63 (20%)	55 (17%)
Decreased appetite	61 (19%)	50 (15%)
Peripheral edema*	57 (18%)	53 (16%)
Abdominal pain*	53 (17%)	67 (21%)
Dizziness*	50 (16%)	38 (12%)
Dyspnea*	49 (16%)	44 (13%)
Cough*	48 (15%)	51 (16%)
Thrombocytopenia*	44 (14%)	17 (5%)
Pain	37 (12%)	42 (13%)
Pain in extremity	36 (11%)	42 (13%)
Local administration reactions*	34 (11%)	27 (8%)
Flushing	32 (10%)	27 (8%)

*Grouped Terms

**Study 1 and Study 2 were not designed to evaluate meaningful comparisons of the incidence of adverse reactions in the Rolvedon™ and the pegfilgrastim treatment groups.

WARNINGS & PRECAUTIONS

Splenic Rupture

Splenic Rupture Splenic rupture, including fatal cases, can occur following the administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) products, such as Rolvedon™. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Rolvedon™.

Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome Acute respiratory distress syndrome (ARDS) can occur in patients receiving rhG-CSF products, such as Rolvedon™. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Rolvedon for ARDS. Discontinue Rolvedon™ in patients with ARDS.

Serious Allergic Reactions
Serious Allergic Reactions Serious allergic reactions, including anaphylaxis, can occur in patients receiving rhG-CSF products, such as Rolvedon™. Permanently discontinue Rolvedon™ in patients with serious allergic reactions. Rolvedon™ is contraindicated in patients with a history of serious allergic reactions to eflapegrastim, pegfilgrastim, or filgrastim products.

Sickle Cell Crisis in Patients with Sickle Cell Disorders
Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving rhG-CSF products, such as Rolvedon™. Discontinue Rolvedon™ if sickle cell crisis occurs.

Glomerulonephritis
Glomerulonephritis has occurred in patients receiving rhG-CSF 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 rhG-CSF. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Rolvedon™.

Leukocytosis
White blood cell (WBC) counts of 100 x 10^9 /L or greater have been observed in patients receiving rhG-CSF products. Monitor complete blood count (CBC) during Rolvedon™ therapy. Discontinue Rolvedon™ treatment if WBC count of 100 x 10^9 /L or greater occurs.

Thrombocytopenia
Thrombocytopenia has been reported in patients receiving rhG-CSF products. Monitor platelet counts.

Capillary Leak Syndrome
Capillary leak syndrome has been reported after administration of rhG-CSF products and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency and 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 Rolvedon™ acts has been found on tumor cell lines. The possibility that Rolvedon™ acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which Rolvedon™ is 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 rhG-CSF 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
Aortitis has been reported in patients receiving rhG-CSF 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, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue Rolvedon™ if aortitis is suspected.

Nuclear Imaging

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

CONTRAINDICATIONS

Rolvedon™ is contraindicated in patients with a history of serious allergic reactions to eflapegrastim, pegfilgrastim, or filgrastim products. Reactions may include anaphylaxis.

Clinical Pharmacology

MECHANISMS OF ACTION

Eflapegrastim-xnst is a recombinant human granulocyte growth factor that binds to G-CSF receptors on myeloid progenitor cells and neutrophils, triggering signaling pathways that control cell differentiation, proliferation, migration and survival.

Dose & Administration

ADULTS

The recommended dosage of Rolvedon™ is a single subcutaneous injection of 13.2 mg administered once per chemotherapy cycle. Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer within the period from 14 days before to 24 hours after administration of cytotoxic chemotherapy.

PEDIATRICS

None.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 13.2 mg/0.6 mL as a clear, colorless, preservative-free solution in a single-dose prefilled syringe.