NEW DRUG APPROVAL

Brand Name	Releuko®
Generic Name	filgrastim-ayow
Drug Manufacturer	Kashiv Biosciences LLC

New Drug Approval

FDA approval date: February 25, 2022

Review designation: N/A

Type of review: Biological License Application (BLA): 761082

Dispensing restriction: Specialty

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Neutrophils play an essential role in immune defenses because they ingest, kill, and digest invading microorganisms, including fungi and bacteria. Failure to carry out this role leads to immunodeficiency, which is mainly characterized by the presence of recurrent infections. Defects in neutrophil function can be quantitative, as seen in neutropenia or qualitative, as seen in neutrophil dysfunction. The standard circulating neutrophil count is above 1.5 x 10/L. Neutropenia can be classified in asymptomatic (mild), moderate, and severe, and thus, the progression to infection concerning the number.

Neutropenia, with decreased production with marrow hypoplasia, can be primary and due to chronic benign neutropenia, cyclical neutropenia, and other congenital and familial neutropenias. It can be secondary to cytotoxic drugs, aplastic anemia, leukemia, drug reactions, and infections. Neutropenia, with increased destruction with marrow hyperplasia, is due to hypersplenism and immune neutropenia. Secondary causes are the commonest. For example, neutropenia caused as a side effect of chemotherapy for malignancies. Congenital forms are rare and vary in severity; some of them are life-threatening conditions including leukocyte adhesion deficiency, Chediak-Higashi syndrome, hyper-IgE, recurrent infection syndrome, and chronic granulomatous disease.

Hsieh and collaborators reported that in the United States, the prevalence of neutropenia was 0.38% among Mexican-Americans, 0.79% among whites, and 4.5% among black participants. Weycker and collaborators reported that the risk of febrile neutropenia during the chemotherapy regimen course for treating solid tumor was 16.8%. Severe neutropenia was present in 1 of every 2 patients with lymphoma receiving chemotherapy with a higher risk of febrile neutropenia, and it was found in approximately 1 of every 10 breast cancer patients in Spain.

Febrile neutropenia (FN) is one of the most common adverse events associated with the administration of myelosuppressive chemotherapy for cancer treatment. There are several definitions of FN; according to the European Society for Medical Oncology (ESMO), FN is defined as: ‘An oral temperature of >38.5°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/l or expected to fall $<0.5 \times 10^9$/l’. An adverse effect of myelosuppressive treatment is the reduction of the ANC and a predisposition to infection from bacteria and fungi. The incidence of FN varies between 10 and 50% in solid tumors and is reportedly ≥80% in hematological malignancies. The mortality and comorbidities associated with FN require immediate hospitalization and treatment with antimicrobial agents. The FN patient group is heterogeneous; therefore, the course of the infection and final outcome depend on individual patient factors such as age, tumor type and stage, previous hospitalizations, or severe comorbidities.

Acute myeloid leukemia (AML) is a malignant disorder of the bone marrow which is characterized by the clonal expansion and differentiation arrest of myeloid progenitor cells. The age-adjusted incidence of AML is 4.3 per 100,000 annually in the United States (US). Incidence increases with age with a median age at diagnosis of 68 years in the US. The etiology of AML is heterogeneous. In some patients, prior exposure to therapeutic, occupational or environmental DNA-damaging agents is implicated, but most cases of AML remain without a clear etiology. AML is the most common form of acute leukemia in adults and has the shortest survival (5-year survival = 24%).

Efficacy

Patients with Cancer Receiving Myelosuppressive Chemotherapy: The safety and efficacy of filgrastim to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).

In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21 day cycles. Patients were randomized to receive filgrastim (n = 99) at a dose of 230 mcg/m2 (4 to 8 mcg/kg/day) or placebo (n = 111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease. The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an ANC < 1,000/mm3 and temperature > 38.2°C. Treatment with filgrastim resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, 40% for filgrastim-treated patients and 76% for placebo-treated patients ($p < 0.001$). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm3); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy: The safety and efficacy of filgrastim to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, de novo AML (Study 4). In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous filgrastim (n = 259) at a dose of 5 mcg/kg/day or placebo (n = 262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥ 1,000/mm3 for 3 consecutive days or ≥ 10,000/mm3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white blood cell count (65% - 100,000/mm3); 29% unfavorable cytogenetics. The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm3 . Treatment with filgrastim resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, filgrastim-treated patients 14 days, placebo-treated patients 19 days ($p = 0.0001$: difference of 5 days (95% CI: -6.0, -4.0)). There was a reduction in the median duration of intravenous antibiotic use, filgrastimtreated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, filgrastim-treated patients: 20 days versus placebo-treated patients: 25 days. There were no statistically significant differences between the filgrastim and the placebo groups in complete remission rate (69% - filgrastim, 68% - placebo), median time to progression of all randomized patients (165 days filgrastim, 186 days - placebo), or median overall survival (380 days – filgrastim, 425 days – placebo).

Patients with Cancer Undergoing Bone Marrow Transplantation: The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo-controlled trial (Study 10). In Study 6, patients with Hodgkin's disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"), and patients with non-Hodgkin's lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). There were 54 patients randomized 1:1:1 to control, filgrastim 10 mcg/kg/day, and filgrastim 30 mcg/kg/day as a 24-hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin's disease and 31% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm3) occurred in the filgrastim - treated groups versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group [11 days in the combined treatment groups, p = 0.004]). In Study 9, patients with Hodgkin's disease and non-Hodgkin's lymphoma received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"). There were 43 evaluable patients randomized to continuous subcutaneous infusion filgrastim 10 mcg/kg/day (n = 19), filgrastim 30 mcg/kg/day (n = 10) and no treatment (n = 14) starting the day after marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin's disease and 72% non-Hodgkin's lymphoma. The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm3) in the filgrastim-treated groups versus the control group (21.5 days in the control group versus 10 days in the filgrastim-treated groups, p < 0.001). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the filgrastim-treated groups, p < 0.0001). In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive filgrastim 300 mcg/m2 /day (n = 33) or placebo (n = 37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, p < 0.001) and time to recovery of ANC to ≥ 500/mm3 (21 days in the control group and 16 days in the treatment group, p < 0.001).

Patients with Severe Chronic Neutropenia: The safety and efficacy of filgrastim to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with severe neutropenia (Study 7). Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < 500/mm3 on three occasions during a 6-month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < 500/mm3 per cycle. In addition, patients must have experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4-month observation period followed by filgrastim treatment or immediate filgrastim treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia. Filgrastim was administered subcutaneously. The dose of filgrastim was determined by the category of neutropenia. Initial dose of filgrastim:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

The main efficacy endpoint was response to filgrastim treatment. ANC response from baseline (< 500/mm3) was defined as follows:

- Complete response: median ANC > 1,500/mm3
- Partial response: median ANC ≥ 500/mm3 and ≤ 1,500/mm3 with a minimum increase of 100%
- No response: median ANC < 500/mm3

There were 112 of 123 patients who demonstrated a complete or partial response to filgrastim treatment. Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving filgrastim of the following parameters:

- Incidence of infection
- Incidence of fever
- Duration of fever
- Incidence, duration, and severity of oropharyngeal ulcers
- Number of days of antibiotic use

The incidence for each of these 5 clinical parameters was lower in the filgrastim arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although filgrastim substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.

Most common adverse reactions in patients:

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea.
- With AML (≥ 2% difference in incidence) are pain, epistaxis and rash.
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash.
- With severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia.

Safety

ADVERSE EVENTS

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- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash.
- With severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia.

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 and lung infiltrates or respiratory distress for ARDS. Discontinue Releuko® in patients with ARDS.
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Releuko® in patients with serious allergic reactions.
- Fatal sickle cell crises: Discontinue Releuko® if sickle cell crisis occurs.
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Releuko® if causality is likely
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Monitor patients with breast and lung cancer using Releuko® in conjunction with chemotherapy and/or radiotherapy for signs and symptoms of MDS/AML.
- Thrombocytopenia: Monitor platelet counts.

CONTRAINDICATIONS

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim products or pegfilgrastim products.

Clinical Pharmacology

MECHANISMS OF ACTION

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. Endogenous G-CSF is a lineage-specific colony-stimulating factor that is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production or activity of hematopoietic cell types other than the neutrophil lineage

Dose & Administration

ADULTS

Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion.

Patients with cancer undergoing bone marrow transplantation - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours.

Patients with congenital neutropenia - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily.

Patients with cyclic or idiopathic neutropenia - Recommended starting dose is 5 mcg/kg subcutaneous injection daily.

Direct administration of less than 0.3 mL (180 mcg) using Releuko® prefilled syringe is not recommended due to potential for dosing errors.

Table 1. Recommended Dosage Adjustments during Neutrophil Recovery in Patients with Cancer Following BMT

Absolute Neutrophil Count	RELEUKO Dosage Adjustment
When ANC greater than 1,000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day[a]
Then, if ANC remains greater than 1,000/mm^3 for 3 more consecutive days	Discontinue RELEUKO
Then, if ANC decreases to less than 1,000/mm^3	Resume at 5 mcg/kg/day

[a] If ANC decreases to less than 1,000/mm^3 at any time during the 5 mcg/kg/day administration, increase RELEUKO to 10 mcg/kg/day, and then follow the above steps.

PEDIATRICS

Refer to adult dosing.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment is required.

HEPATIC IMPAIRMENT

No dosage adjustment is required.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Vial:

- Injection: 300 mcg/mL in a single-dose vial
- Injection: 480 mcg/1.6 mL in a single-dose vial

Prefilled Syringe:

- Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe
- Injection: 480 mcg/0.8 mL in a single-dose prefilled syringe