CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761082Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 25, 2022
To:	Courtney Hamilton, PharmD, BCPS Regulatory Project Manager **Division of NonMalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (nonproprietary name):	[Theragrastim] RELEUKO (filgrastim-ayow)[1]
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761082
Applicant:	Kashiv BioSciences, LLC

[1] Theragrastim has been developed as a proposed biosimilar to US-licensed Neupogen (filgrastim). The proposed proprietary name RELEUKO was found to be conditionally acceptable by DMEPA on November 8, 2021. The nonproprietary name, filgrastim-ayow, was found to be conditionally acceptable by DMEPA on October 7, 2021.

1 INTRODUCTION

On August 27, 2021, Kashiv BioSciences, LLC re-submitted for the Agency's review an original Biologics License Application (BLA) 761082 for RELEUKO (filgrastim-ayow) injection, a proposed biosimilar to US-licensed NEUPOGEN (filgrastim) injection (BLA 103353). This submission is a Complete Response (CR) in response to the Agency's CR letter dated August 2, 2021. The proposed indications for RELEUKO (filgrastim-ayow) injection are as follows:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti- cancer drugs associated with a significant incidence of severe neutropenia with fever.
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
- Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of NonMalignant Hematology (DNH) on October 18, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for RELEUKO (filgrastim-ayow) injection. On January 10, 2022, the Agency requested the Applicant to more closely align the proposed IFUs with US-licensed NEUPOGEN (filgrastim) injection, single-dose vial and prefilled syringe IFUs. Our collaborative review of the RELEUKO (filgrastim-ayow) injection PPI was completed on January 13, 2022.

2 MATERIAL REVIEWED

- Draft RELEUKO (filgrastim-ayow) injection, single-dose vial IFU received on January 17, 2022, and received by DMPP and OPDP on January 18, 2022.
- Draft RELEUKO (filgrastim-ayow) injection, single-dose prefilled syringe IFU received on February 2, 2022, and received by DMPP and OPDP on February 2, 2022.
- Draft RELEUKO (filgrastim-ayow) injection Prescribing Information (PI) received on August 27, 2021, and revised by the Review Division throughout the review cycle.
- Approved US-licensed NEUPOGEN (filgrastim) injection IFU dated June 29, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFUs, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU documents using the Arial font, size 10.

In our collaborative review of the IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFUs are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFUs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

- The IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFUs.

Please let us know if you have any questions.

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/s/

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SHARON R MILLS
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Division of Nonmalignant Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	Proposed: **RELEUKO (filgrastim-ayow) injection, for subcutaneous or intravenous use.**
Applicant	Kashiv Biosciences
Application/Supplement Number	BLA 761082
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Approved Indication(s)	RELEUKO is a leukocyte growth factor indicated to: •Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. •Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). •Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). •Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
Date FDA Received Application	08/27/2021
Review Classification (Priority/Standard)	Standard
Action Goal Date	02/27/2022
Review Date	02/22/2022
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.

[3] See *PLR Requirements for PI* website for PLR labeling guidances.

- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: Kashiv Biosciences initially submitted their biosimilar application on 07/08/2017. FDA issued a complete response (CR) on 05/10/2018 due to deficiencies at the Adello Biologics manufacturing facility and multiple product deficiencies. The Applicant submitted a Class 2 resubmission on 12/11/2018, for which a CR was again issued on 06/11/2019 for deficiencies at the Kashiv BioSciences manufacturing facilities and continued product deficiencies. The Applicant submitted a Class 2 resubmission on 06/24/2020, for which a CR was again issued on 12/22/2020 for deficiencies at the Kashiv Biosciencies manufacturing facility as well as product deficiencies. On 2/2/21, Kashiv submitted a Class 2 resubmission which again received a CR on 08/02/21. This submission constitutes their most recent Class 2 resubmission.

Review Summary of Revisions to Applicant Proposed Labeling

Throughout the USPI:

- Revised labeling text to be consistent with the reference biological product (Neupogen) when possible, with exceptions for biosimilar product differences.
- Changed "single-use" to "single-dose" per the FDA Guidance: "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple - Dose, Single-Dose, and Single-Patient-Use Containers for Human Use". http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf
- Added "products" when referring to all filgrastim products.
- Used "RELEUKO" in statements directing action with the product.

Highlights:

- Removed "limitations of use" for autologous mobilization and HSARS (indications not requested due to existing exclusivity/patents) per Biosimilar Labeling Guidance.
- Removed "Use in Specific Populations" subheading for Pregnancy (not present in Neupogen USPI)
- Other edits to Highlights are regarding changes to the Full Prescribing Information (FPI) and thus noted in those sections.

Table of Contents: Removed Section 15 References (it was deleted in USPI).

Full Prescribing Information:

1) Indications and Usage: No change.

2) Dosage and Administration: Revised text regarding visual inspection of parenteral drug products to be consistent with the labeling regulations (21CFR201.57) which require this verbatim statement, as well as to be consistent with the reference biological product labeling.

   DMEPA added to 2.4 "Patient self-administration and administration by a caregiver may benefit from training by a healthcare professional."

   DMEPA added to 2.4 "The RELUEKO prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is

necessary to accurately measure doses of RELEUKO less than 0.3 mL (180 mcg) for direct administration. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors. For direct administration of doses less than 0.3 mL (180 mcg) use RELUEKO single-dose vial." To alert users that the prefilled syringe cannot be used to measure doses less than 0.3 mL.

FDA deleted text in 2.4 [redacted] (b) (4)

The acceptable storage time for diluted RELEUKO solution (for infusion) was reduced to 4 hours, as supported by data submitted in the application and other information before the Agency (see the Addendum to the OPQ Executive Summary). The sentence [redacted] (b) (4) " was deleted because it is not relevant to this product and the OPMA review staff indicated that the 4-hour storage time is acceptable and that statements in labeling do not typically include infusion time.

3) Dosage Forms and Strengths: Changed "single-use" to "single-dose" per the FDA Guidance: "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use".
4) Contrainidications: Revised "Filgrastim products are" to "RELEUKO is" as the contraindication statement is about this product.

5) Warnings and Precautions: Revised text of Warning 5.4 (Sickle Cell Disorder) to be consistent with Reference Product USPI, as per the Biosimilar Labeling Guidance. Removed subsection "Peripheral Blood Progenitor Cell Collection and Therapy" as it relates to an indication not being sought by the Applicant. Also removed similar text in Warning 5.12 Potential Effect on Malignant Cells.

6) Adverse Reactions: Added word "clinical" to first sentence in 6.1 to be consistent with Reference Product labeling and the Biosimilar Labeling guidance. In section 6.2, first paragraph was revised to be consistent with the Biosimilar Products guidance. In section 6.3, the word "Precautions" was misspelled as "Precautious" and corrected.

7) Drug Interactions: Section omitted.

8) Use in Specific Populations: In Section 8.1 Pregancy, FDA deleted [redacted] (b) (4) In Section 8.4 Pediatric Use, FDA added the text: "RELEUKO prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard may not accurately measure volumes less than 0.3 mL due to the needle spring mechanism design. Therefore, the direct administration of a volume less than 0.3 mL using RELEUKO prefilled syringe is not recommended due to the potential for dosing errors. For direct administration of doses less than 0.3 mL (180 mcg) use RELEUKO single-dose vial." To call attention to the limitations of the prefilled syringe ability to accurately measure volumes less than 0.3 mL. Section 8.5 was modified to remove reference to "PBPC mobilization" so as to avoid referring to a non-indicated use.

9) Omitted

10) Overdosage: No changes.

11) Description: In the first sentence, just after the product name, the established pharmacologic class (EPC) "a leukocyte growth factor" was added per Per 21CFR201.57(a)(6). Several changes specific to the RELEUKO product, such as content of kanamycin, were added. The route of administration "for subcutaneous or intravenous use" was also added per 21CFR201.57(c)(12).

12) Clinical Pharmacology: No changes.

13) Nonclinical Toxicology: No changes.

14) Clinical Studies: Section 14.2, added "blood cell" to be consistent with Reference Product labeling. Minor edits to add missing words in description of the studies to be consistent with Reference Product Labeling.

15) References: Deleted section to be consistent with deletions in section 8 and to be consistent with Reference Product labeling.

16) How Supplied/Storage and Handling: Added "filgrastim-ayow" to add non-proprietary name with suffix.

17) Patient Counseling Information: Removed bullet for females of reproductive potential to be consistent with Reference Product labeling. Added the following text to bullet describing the importance of informing HCP if difficulty occurs when measuring partial contents of the prefilled syringe "If difficulty occurs, use of the RELEUKO vial may be considered." Added this text: "Difference in product concentration of the RELEUKO prefilled syringe in comparison to the RELEUKO vial. When switching patients from the RELEUKO prefilled syringe to the RELEUKO vial, or vice versa, ensure that patients understand the correct volume to be administered since the concentration of RELEUKO differs between the prefilled syringe and the vial." to be consistent with Reference Product labeling.

Regulatory Recommendation: Labeling negotiations are complete. From the labeling perspective, BLA 761082 is recommended for approval.

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/s/

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 18, 2022
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761082
Product Name, Dosage Form, and Strength:	Theragrastim (rhG-CSF)[a] Releuko (filgrastim-ayow) injection Vials: 300 mcg/mL, 480 mcg/1.6 mL Prefilled syringes: 300 mcg/0.5 mL, 480 mcg/0.8 mL
Product Type:	Single Component Product; Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Kashiv BioSciences, LLC
FDA Received Date:	August 27, 2021, December 16, 2021, January 20, 2022, February 2, 2022, and February 14, 2022
OSE RCM #:	2017-1428-1
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

[a] Theragrastim (rhG-CSF) has been developed as a proposed biosimilar to US-licensed Neupogen (filgrastim). The proposed proprietary name, Releuko, was found conditionally acceptable on November 3, 2021. The nonproprietary name, filgrastim-ayow, was found conditionally acceptable on October 7, 2021.

1 REASON FOR REVIEW

Kashiv BioSciences, LLC (Kashiv) submitted a response to complete response for Releuko (filgrastim-ayow), BLA 761082 on August 27, 2021. This review evaluates the proposed container labels, carton labeling, Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for Releuko (filgrastim-ayow) for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT BACKGROUND

Releuko is a proposed biosimilar to the US-licensed Neupogen (BLA 103353). US-licensed Neupogen (filgrastim) was approved on February 20, 1991, as a leukocyte growth factor. US-licensed Neupogen has 6 approved indications. Releuko is being proposed for four of the same indications as US-licensed Neupogen, with the exception of the indications for mobilizing autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis and increasing survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).

US-licensed Neupogen is supplied as 300 mcg and 480 mcg single-dose vials and single-dose, graduated prefilled syringes with manual needle guards. Releuko proposes to be supplied as 300 mcg and 480 mcg single-dose vials and single-dose, graduated prefilled syringes with passive needle guards.

1.2 REGULATORY HISTORY

BLA 761082 was originally submitted on July 10, 2017, however, the application received a Complete Response (CR) letter on May 10, 2018 due to facility inspections and product quality issues. The CR letter explained that FDA reserved comment on the proposed labeling until the application is otherwise adequate.

Kashiv then submitted a response to the CR letter for BLA 761082 on December 11, 2018; however, the application again received a CR letter on June 11, 2019 due to facility inspections and product quality issues. Again, the Agency reserved comment on the proposed labeling.

Kashiv submitted a response to the CR letter for BLA 761082 on February 2, 2021. DMEPA completed a review of the use-related risk analysis (URRA), physical comparison, and IFU comparison of the proposed product with US-licensed Neupogen and label labeling review on June 7, 2021.[b] The application received a CR letter on August 2, 2021 due to facility inspection and product quality deficiencies. Again, the Agency reserved comment on the proposed labeling.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

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[b] DeGraw, S. Releuko (filgrastim-ayow) URRA CA Label Labeling Review. Silver Spring (MD): FDA, CDER, DNH (US); 2021 JUN 7. RCM No.: 2017-1428.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, PI, Patient Information (PPI), and Instructions for Use (IFU) for Releuko to identify deficiencies that may lead to medication errors and other areas of improvement.

Our evaluation of the proposed PI, IFUs, container labels and carton labeling identified several areas that can be improved to increase the readability and prominence of important information. We provide recommendations for the PI and pre-filled syringe IFU below.

Our recommendations for the container labels and carton labeling were sent to Kashiv via information request on December 3, 2021 (see Appendix F). On December 16, 2021, Kashiv submitted revised container label and carton labeling. Additionally, Kashiv submitted revised vial and pre-filled syringe carton labeling and 480 mcg/0.8 mL pre-filled syringe tray labeling on January 20, 2022 and vial carton labeling and vial container label February 14, 2022 based on recommendations from Office of Biologic Products (OBP). The revised container labels and carton labeling are acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

Our review of the proposed PI and pre-filled syringe IFU identified several areas that can be improved to increase the readability and prominence of important information. We provide recommendations for the Division in section 4.1 to be implemented prior to approval of BLA 761082.

We conclude the container labels, carton labeling, vial IFU, and PPI are acceptable from a medication error perspective. We have no recommendations at this time. We defer to the Patient Labeling Team (PLT) for recommendations for the PPI.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

Prescribing Information

A. Highlights
    1. Dosage and Administration
        a. We recommend adding an additional bullet point with the following information to alerts users that the prefilled syringe cannot be used to measure doses less than 0.3 mL: “Direct administration of less than 0.3 mL (180 mcg) using RELEUKO prefilled syringe is not recommended due to potential for dosing errors. (2.4)”

B. Full Prescribing Information
    1. Important Administration Instructions [2.4]
        a. We recommend adding “Patient self-administration and administration by a caregiver may benefit from training by a healthcare professional.” as the first sentence in the paragraph pertaining to training.
        b. We recommend adding the following information to alerts users that the prefilled syringe cannot be used to measure doses less than 0.3 mL: “The RELEUKO prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of RELEUKO less than 0.3 mL (180 mcg) for direct administration. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors. For direct administration of doses less than 0.3 mL (180 mcg) use RELEUKO single-dose vial.”.

C. Pediatric Use [8.4]
    1. We recommend adding the following information to alerts users that the prefilled syringe cannot be used to measure doses less than 0.3 mL: “RELEUKO prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard may not accurately measure volumes less than 0.3 mL due to the needle spring mechanism design. Therefore, the direct administration of a volume less than 0.3 mL using RELEUKO prefilled syringe is not recommended due to the potential for dosing errors. For direct administration of doses less than 0.3 mL (180 mcg) use RELEUKO single-dose vial.”

Instructions for Use for the Prefilled Syringe

A. Step 9 Remove the needle cap

1. The image in Figure F, does not match the accompanying text of pulling of the needle cap straight off. As currently presented in the image, the needle cap is removed at an angle. We recommend revising the image to show the pulling of the needle cap straight off.

B. Step 3 Inject the dose
   1. We recommend deleting the bullet point (b) (4)

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Releuko received on May 18, 2021 from Kashiv BioSciences, LLC, and the US-licensed Neupogen.

Table 2. Relevant Product Information for Releuko and US-licensed Neupogen

Product Name	Releuko	US-licensed Neupogen
Initial Approval Date	N/A	February 1991
Nonproprietary/Proper Name	filgrastim-ayow	filgrastim
Indication	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti- cancer drugs associated with a significant incidence of severe neutropenia with fever. • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). • Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti- cancer drugs associated with a significant incidence of severe neutropenia with fever. • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). • Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. • Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis

		• Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).
Route of Administration	Intravenous and subcutaneous	Intravenous and subcutaneous
Dosage Form	Injection	Injection
Strength	Vials • Injection: 300 mcg/mL in a single-use vial • Injection: 480 mcg/1.6 mL in a single-use vial Prefilled Syringes • Injection: 300 mcg/0.5 mL in a single-use prefilled syringe • Injection: 480 mcg/0.8 mL in a single-use prefilled syringe	Vials • Injection: 300 mcg/mL in a single-use vial • Injection: 480 mcg/1.6 mL in a single-use vial Prefilled Syringes • Injection: 300 mcg/0.5 mL in a single-use prefilled syringe • Injection: 480 mcg/0.8 mL in a single-use prefilled syringe
Dose and Frequency	• Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy: 5 mcg/kg/day once daily given as a subcutaneous injection, short intravenous infusion, or continuous intravenous infusion • Bone Marrow Transplantation: 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. • Congenital Neutropenia: 6 mcg/kg/day subcutaneous injection twice per day. • Idiopathic or Cyclic Neutropenia: 5 mcg/kg/day subcutaneous injection daily.	• Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy: 5 mcg/kg/day once daily given as a subcutaneous injection, short intravenous infusion, or continuous intravenous infusion • Bone Marrow Transplantation: 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. • Congenital Neutropenia: 6 mcg/kg/day subcutaneous injection twice per day. • Idiopathic or Cyclic Neutropenia: 5 mcg/kg/day subcutaneous injection daily. • Autologous Peripheral Blood Progenitor Cell Collection and Therapy: 10 mcg/kg/day given as a subcutaneous injection. Administer Neupogen for at least 4 days before the first leukapheresis procedure and

		continue until the last leukapheresis. • Hematopoietic Syndrome of Acute Radiation Syndrome: 10 mcg/kg as a single daily subcutaneous injection.
How Supplied	RELEUKO injection is a clear, colorless, preservative-free solution supplied as: <u>Vials</u> • Single-dose vials containing 300 mcg/mL of filgrastim-ayow. Dispensing packs of 10 vials. • Single-dose vials containing 480 mcg/1.6 mL (300 mcg/mL) of filgrastim-ayow. Dispensing packs of 10 vials. <u>Prefilled Syringes</u> Single-dose, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe Plus™ Needle Guard, containing 300 mcg/0.5 mL of filgrastim-ayow. • Pack of 10 prefilled syringes Single-dose, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe Plus™ Needle Guard, containing 480 mcg/0.8 mL of filgrastim-ayow. • Pack of 10 prefilled syringes	NEUPOGEN injection is a clear, colorless, preservative-free solution supplied as: <u>Vials</u> • Single-dose vials containing 300 mcg/mL of filgrastim. Dispensing packs of 10 vials. • Single-dose vials containing 480 mcg/1.6 mL (300 mcg/mL) of filgrastim. Dispensing packs of 10 vials. <u>Prefilled Syringes</u> Single-dose, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe ® Needle Guard, containing 300 mcg/0.5 mL of filgrastim. • Pack of 1 prefilled syringe • Pack of 10 prefilled syringes Single-dose prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe ® Needle Guard, containing 480 mcg/0.8 mL of filgrastim. • Pack of 1 prefilled syringe • Pack of 10 prefilled syringes
Storage	Store Releuko at 2°C to 8°C (36°F to 46°F) in the pack to protect from light. Do not leave Releuko in direct sunlight. DO NOT freeze Releuko. Avoid shaking. Transport via a pneumatic tube has not been studied.	Store Neupogen at 2°C to 8°C (36°F to 46°F) in the carton to protect from light. Do not leave Neupogen in direct sunlight. Avoid freezing; if frozen thaw in the refrigerator before administration. Discard Neupogen if frozen more than once. Avoid shaking. Transport via a pneumatic tube has not been studied.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 12, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, “Releuko”, “filgrastim-ayow”, “BLA 761082” and “IND 115333”. Our search identified 1 previous reviews[c], and we considered our previous recommendations to see if they are applicable for this current review.

[c] DeGraw, S. Use-Related Risk Analysis, Comparative Analysis, and Label and Labeling Review for Theragrastim (BLA 761082). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 7. RCM No.: 2017-1428.

APPENDIX F. DMEPA RECOMMENDATIONS SENT ON DECEMBER 3, 2021

The following recommendations were communicated to the sponsor, KASHIV BIOSCIENCES, LLC via e-mail on December 3, 2021.

A. All Container Labels and Carton Labeling

1. Revise the strength presentation '300 mcg/1.0 mL' to appear as '300 mcg/mL' in accordance with USP General Chapter <7>.

2. On the carton labeling, add the dosage form "Injection" to appear below the non-proprietary name as follows:

   Releuko
   (filgrastim-ayow)
   Injection

   If space permits, add the dosage form on the syringe and vial labels as well.

3. As currently presented, the format of the expiration date is not indicated. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Vial label

1. To accurately reflect the correct package type term, revise "Single Use Vial" to read "Single-Dose Vial. Discard unused portion."

2. If space allows, we recommend adding the route of administration. For example, "For subcutaneous or intravenous use only".

3. Clarify the significance of the number located next to the lot number and expiration date (b) (4). If it is an internal product code, we recommend removing and/or relocating this number to mitigate the potential for confusion due its proximity to the lot number and expiration date.

C. Syringe label

1. Include the unit of measure (mL) at the last syringe marking (e.g., 0.5 mL or 0.8 mL). We recommend this to mitigate the risk of dosing errors.

2. To accurately reflect the correct package type term, revise "Single Use Prefilled Syringe" to read "Single-Dose Prefilled Syringe."

3. If space allows, we recommend adding the route of administration. For example, “For subcutaneous use only””.

D. Vial carton labeling

1. Ensure that the strength is expressed as total protein content per total volume in the circle on Principal display panel (PDP). See USP General Chapters <7> Labeling. For example, revise the strength presentation to appear as “300 mcg/mL”.

2. Include the statement “Discard unused portion.” to appear after the package type term. To accommodate this change, relocate the statement “Sterile Solution - No Preservative” to the side panel. We recommend this to mitigate the risk of the vial being used to prepare more than one dose.

3. Revise “Single Use Vial” to read “Single-Dose Vial” to reflect the correct package type and relocate to below the route of administration on the principal display panel.

4. Please indicate where the required lot number and expiration date will appear as required per 21 CFR 610.60.

5. Revise and relocate the storage information, “**Store Refrigerated at 2° to 8°C (36° to 46°F).** Do not freeze. Do not shake.” to the side panel.

6. Revise the net quantity statement to remove the “trailing zero” (i.e., 1.0). Revise to read “10 x 1 mL Single-dose Vials”.

7. Include the dosage statement, “Dosage: See Prescribing Information” on the side or back panel in accordance with 21 CFR 201.55.

8. As currently presented, the inclusion of a product identifier is not indicated. In September 2018, FDA released draft guidance, which, when finalized will represent the agency’s current thinking on the topics therein, on product identifiers required under the Drug Supply Chain Security Act.[d] The Act requires manufacturers and re-packagers, respectively, to affix or imprint a human-readable and machine-readable product identifier to each package and

[d] Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018.
Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. Therefore, please confirm the inclusion and location of this information.

E. Syringe carton labeling ((b) (4) tray)

1. Ensure that the strength is expressed as total protein content per total volume in the circle on Principal display panel (PDP). See USP General Chapters <7> Labeling. For example, revise the strength presentation to appear as "300 mcg/0.5 mL".

2. To accurately reflect the correct package type term, revise "Single Use Prefilled Syringe" to read "Single-Dose Prefilled Syringe".

3. Please indicate where the required lot number and expiration date will appear as required per 21 CFR 610.60.

4. Per the Prescribing Information, the prefilled syringe should only be used for subcutaneous administration. As such, revise the route of administration statement to read "For Subcutaneous Use Only."

5. Revise "Read the full prescribing information before use" to read "Dosage: See Prescribing Information" in alignment with 21 CFR 201.55 to ensure consistency with all doses described in the prescribing information.

6. As currently presented, the inclusion and location of a linear barcode is not indicated. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label. Add the product's linear barcode to each individual carton (tray) labeling in accordance with 21 CFR 201.25(c)(2).

F. Syringe carton labeling (outer carton)

1. See E.1 through E.4 and revise the carton labeling accordingly.

2. Include the dosage statement, "Dosage: See Prescribing Information" on the side or back panel in accordance with 21 CFR 201.55.

3. As currently presented, the inclusion of a product identifier is not indicated. In September 2018, FDA released draft guidance, which, when finalized will represent the agency's current thinking on the topics therein, on product identifiers required under the Drug Supply Chain Security Act.[e] The Act requires

[e] Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018.

manufacturers and re-packagers, respectively, to affix or imprint a human-readable and machine-readable product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. Therefore, please confirm the inclusion and location of this information.

4. Revise and relocate the storage information, "**Store Refrigerated at 2° to 8°C (36° to 46°F).** Do not freeze. Do not shake." to the side panel.

Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Releuko labels and labeling submitted by Kashiv BioSciences, LLC.

- Container label received on December 16, 2021 and February 14, 2022
- Carton labeling received on December 16, 2021, January 20, 2022, and February 14, 2022
- Syringe Instructions for Use (Image not shown) received on February 2, 2022 , 2022, available from \\CDSESUB1\evsprod\bla761082\0072\m1\us\114-labeling\draft-labeling\draft-label-text\draft-pfs-ifu-pdf.pdf
- Vial Instructions for Use (Image not shown) received on February 2, 2022, available from \\CDSESUB1\evsprod\bla761082\0072\m1\us\114-labeling\draft-labeling\draft-label-text\draft-vial-ifu-word-track-change.docx
- Prescribing Information (Image not shown) received on May 18, 2021, available from \\CDSESUB1\evsprod\bla761082\0058\m1\us\114-labeling\draft-labeling\draft-label-text\draft-labeling-prescribing-info.pdf

G.2 Label and Labeling Images

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 13, 2022
To:	Courtney Hamilton, PharmD, BCPS Regulatory Project Manager **Division of NonMalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (nonproprietary name):	[Theragrastim] RELEUKO (filgrastim-ayow)[1]
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761082
Applicant:	Kashiv BioSciences, LLC

[1] Theragrastim has been developed as a proposed biosimilar to US-licensed Neupogen (filgrastim). The proposed proprietary name RELEUKO was found to be conditionally acceptable by DMEPA on November 8, 2021. The nonproprietary name, filgrastim-ayow, was found to be conditionally acceptable by DMEPA on October 7, 2021.

1 INTRODUCTION

On August 27, 2021, Kashiv BioSciences, LLC re-submitted for the Agency's review an original Biologics License Application (BLA) 761082 for RELEUKO (filgrastim-ayow) injection, a proposed biosimilar to US-licensed NEUPOGEN (filgrastim) injection (BLA 103353). This submission is a Complete Response (CR) in response to the Agency's CR letter dated August 2, 2021. The proposed indications for RELEUKO (filgrastim-ayow) injection are as follows:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti- cancer drugs associated with a significant incidence of severe neutropenia with fever.
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
- Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of NonMalignant Hematology (DNH) on October 18, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for RELEUKO (filgrastim-ayow) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs will be forthcoming.

2 MATERIAL REVIEWED

- Draft RELEUKO (filgrastim-ayow) injection PPI received on August 27, 2021, and received by DMPP and OPDP on November 16, 2021.
- Draft RELEUKO (filgrastim-ayow) injection Prescribing Information (PI) received on August 27, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 16, 2021.
- Approved US-licensed NEUPOGEN (filgrastim) injection PI dated February 4, 2021 and PPI dated January 5, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

- The PPI is acceptable with our recommended changes.
- Agency plans to request that the Applicant more closely align their IFUs with US-licensed NEUPOGEN (filgrastim) injection, single-dose vial and prefilled syringe IFUs. We defer review of the RELEUKO (filgrastim-ayow) injection, single-dose vial and prefilled syringe IFUs at this time. We will complete a collaborative review of the Applicant's revised single-dose vial and prefilled syringe IFUs after they have been submitted to the BLA.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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SHARON R MILLS
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LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 18, 2021

To: Courtney Hamilton, PharmD, BCPS, Regulatory Project Manager, Division of Non-malignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for RELEUKO (filgrastim-ayow) injection, for subcutaneous or intravenous use

BLA: 761082

In response to DNH's consult request dated October 18, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and Instructions for Use (IFU), and for the original BLA resubmission for RELEUKO (filgrastim-ayow) injection, for subcutaneous or intravenous use (Releuko). Per communications by electronic mail with Courtney Hamilton on November 16, 2021, OPDP has reviewed the proposed carton and container labeling as well.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Courtney Hamilton) on November 16, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 27, 2021, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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USE-RELATED RISK ANALYSIS, COMPARATIVE ANALYSIS, AND LABEL & LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 7, 2021
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	BLA 761082
Product Name and Strength:	Theragrastim[a] Releuko (filgrastim-ayow) injection Vials: 300 mcg/mL, 480 mcg/1.6 mL Prefilled syringes: 300 mcg/0.5 mL, 480 mcg/0.8 mL
Product Type:	Single Component Product; Combination Product (Biologic-Device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Kashiv BioSciences, LLC (Kashiv)
Submission Dates:	July 10, 2017, September 27, 2017, January 5, 2018, and February 2, 2021
OSE RCM #:	2017-1428
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Chi-Ming (Alice) Tu, PharmD

[a] Theragrastim has been developed as a proposed biosimilar to US-licensed Neupogen (filgrastim). The proposed proprietary name (Releuko) and proposed nonproprietary name (filgrastim-ayow) are only conditionally accepted for this product until the application is approved.

1 REASON FOR REVIEW

Kashiv BioSciences, LLC (Kashiv) submitted a Class 2 Resubmission for BLA 761082 for Releuko (filgrastim-ayow) on February 2, 2021. This review evaluates the proposed container labels, carton labeling, Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for Releuko (filgrastim-ayow) for areas of vulnerability that could lead to medication errors. In addition, we evaluated the use-related risk analysis (URRA) and comparative analyses (CA) previously submitted by Kashiv on September 27, 2017 and January 5, 2018.

1.1 PRODUCT BACKGROUND

Releuko is a proposed biosimilar to the US-licensed Neupogen (BLA 103353). US-licensed Neupogen (filgrastim) was approved on February 20, 1991, as a leukocyte growth factor. US-licensed Neupogen has 6 approved indications. Releuko is being proposed for four of the same indications as US-licensed Neupogen, with the exception of the indications for mobilizing autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis, and increasing survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).

US-licensed Neupogen is supplied as 300 mcg and 480 mcg single-dose vials and single-dose, graduated prefilled syringes with manual needle guards. Releuko proposes to be supplied as 300 mcg and 480 mcg single-dose vials and single-dose, graduated prefilled syringes with passive needle guards.

1.2 REGULATORY HISTORY

BLA 761082 was originally submitted on July 10, 2017, however, the application received a Complete Response (CR) letter on May 10, 2018 due to facility inspections and product quality issues. The CR letter explained that FDA reserved comment on the proposed labeling until the application is otherwise adequate.

Kashiv then submitted a response to the CR letter for BLA 761082 on December 11, 2018; however, the application again received a CR letter on June 11, 2019 due to facility inspections and product quality issues. Again, the Agency reserved comment on the proposed labeling.

On June 1, 2020, Kashiv submitted a request for an extension to resubmit BLA 761082 in response to our complete response letter dated June 11, 2019. The Agency granted a 6-month extension to resubmit the application.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Human Factors – Use Related Risk Analysis and Threshold Analysis	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search ISMP Newsletter or FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Kashiv resubmitted their 351(k) application for Releuko (filgrastim-ayow) injection. We evaluated the URRA, CA, proposed container labels, carton labeling, Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for Releuko (filgrastim-ayow) injection.

3.1 USE-RELATED RISK ANALYSIS ASSESSMENT

We note that Releuko has the same intended users, use environments, dosing, route of administration, strength, and storage requirements as US-licensed Neupogen.

To support the review of the proposed PFS presentation, Kashiv submitted a URRA and CA as a part of the original BLA submission on July 10, 2017, September 27, 2017, and January 5, 2018 (see Appendix F). Along with the URRA the Applicant submitted justification for not completing a human factors (HF) validation study for the proposed prefilled syringe (PFS).

The URRA identified and evaluated the tasks involved in the use of Releuko PFS, the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors.

We reviewed the URRA for the proposed product. We did not identify any new or unique risks for the Releuko PFS as compared to the US-licensed Neupogen PFS. However, we note that users are not required to activate the needle guard manually (as compared to the US-licensed Neupogen PFS). We describe our evaluation of this difference below (see Section 3.3).

3.2 COMPARATIVE ANALYSES ASSESSMENT

Physical Comparison of the Prefilled Syringes

Releuko is supplied as a single-dose, prefilled syringe (PFS) with an UltraSafe Plus™ passive needle guard and single-dose vials. US-licensed Neupogen is supplied as a single-dose, PFS with a manual needle guard and single-dose vials.

We note in the physical comparison that the Releuko PFS plunger has a larger head and finger grips when compared to the US-licensed Neupogen PFS. Additionally, Releuko PFS has a clear

(transparent) UltraSafe Plus™ passive needle guard while US-licensed Neupogen has a transparent orange UltraSafe Active needle guard. In this particular instance, our evaluation of the physical comparison determined the physical differences should not affect critical tasks, therefore, these differences are acceptable.

Task Comparison for the Prefilled Syringes

We note in the task comparison, that the critical tasks for Releuko align with the critical tasks for US-licensed Neupogen, with one exception that users of the US-licensed Neupogen PFS are required to activate the needle guard manually (i.e. the user slides the needle guard over the needle), whereas, Releuko has a passive needle guard which does not require manual activation. The passive needle guard automatically activates after the user presses the plunger all the way down to administer the injection and then allows their finger to release pressure, which causes the needle to retract into the body and lock the guard in place. We find the elimination of the manual activation of the needle guard in Releuko acceptable.

Labeling Comparison: Side-by-Side IFU Comparison for the Prefilled Syringes

The proposed Releuko PFS IFU follows similar steps and injection technique as the US-licensed Neupogen PFS IFU. However, we note the following differences related to the passive needle guard which we find acceptable:

- The safety device (passive needle guard) of the Releuko PFS has a stainless-steel spring mechanism that helps trigger and activate the safety device. Unlike US-licensed Neupogen, there is low visibility of the graduation markings on the syringe barrel at 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of less than 0.3 mL (180 mcg) for direct administration to patients. Based on this limitation, the proposed Releuko IFU instructs users that direct administration to patients requiring less than 0.3 mL (180 mcg) is not recommended with the proposed PFS due to the potential for dosing errors. For patients who require doses less than 0.3 mL (180 mcg), Releuko vials may be used.
- The step describing activation of the needle guard differs from US-licensed Neupogen due to the differences in the needle guard design (passive vs. manual).

We also note the other following differences:

- Storage information is not presented as part of the important information section.
- Figure G in the Releuko IFU does not include labels for the appropriate injection sites, unlike the US-licensed Neupogen IFU.
- Additionally, we identified other aspects of the IFU that should be revised to add and/or relocate important information regarding the administration of Releuko.

We provide all recommendations for the IFU in Section 4.1 below.

3.3 LABELS AND LABELING

DMEPA performed a risk assessment of the container labels, carton labeling, prescribing information (PI), patient information (PPI), and IFUs to identify deficiencies that may lead to

medication errors. We determined the proposed PI and patient package insert contain language consistent with US-licensed Neupogen; however, we note that language explaining that the prefilled syringe should not be used to measure doses less than 0.3 mL should be added to *Highlights – Dosage and Administration* and sections *2.4 Important Administration Instructions* and *8.4 Pediatric Use* of the PI. We provide this recommendation in section 4.1 below.

The proposed Releuko prefilled syringe IFU can be improved to include important storage information and to increase clarity of instructions and figure images. The proposed Releuko vial IFU can be improved to include important storage information, to remove error-prone abbreviations, and to increase the clarity of instructions and figure images.

Our review of the PPI determined the PPI is acceptable from a medication error perspective and as such, we have no concerns or recommendations at this time.

The proposed container labels and carton labeling can be improved to state correct package type terms, to include and/or increase readability and prominence of the route of administration, strength presentation, usual dosage, storage, net quantity statement, and product identifiers. We provide recommendations for the container labels and carton labeling in section 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds that Kashiv has adequately considered the risks associated with the proposed single-dose prefilled syringe when compared to the US-licensed Neupogen (filgrastim). We agree the Applicant does not need to submit a human factors validation study for the Agency's review at this time.

Our review of the proposed PI, IFUs, container labels and carton labeling identified several areas that can be improved to increase the readability and prominence of important information. We provide recommendations for the Division in section 4.1 and for the Applicant in section 4.2 to be implemented prior to approval of BLA 761082.

We conclude the PPI is acceptable from a medication error perspective. We have no recommendations at this time. We defer to the Patient Labeling Team (PLT) for recommendations for the PPI.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. Highlights
    1. Dosage and Administration
        a. We recommend adding an additional bullet point with the following information to alerts users that the prefilled syringe cannot be used to measure doses less than 0.3 mL: "Direct administration of less than 0.3 mL (180 mcg) using RELEUKO prefilled syringe is not recommended due to potential for dosing errors. (2.4)"

B. Important Administration Instructions [2.4]
    1. Administration Instructions for the Prefilled Syringe
        a. We recommend adding the following information to alerts users that the prefilled syringe cannot be used to measure doses less than 0.3 mL: “The RELUEKO prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of RELEUKO less than 0.3 mL (180 mcg) for direct administration. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors. For direct administration of doses less than 0.3 mL (180 mcg) use RELUEKO single-dose vial.

C. Pediatric Use [8.4]
    1. We recommend adding the following information to alerts users that the prefilled syringe cannot be used to measure doses less than 0.3 mL: “RELEUKO prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard may not accurately measure volumes less than 0.3 mL due to the needle spring mechanism design. Therefore, the direct administration of a volume less than 0.3 mL using RELEUKO prefilled syringe is not recommended due to the potential for dosing errors. For direct administration of doses less than 0.3 mL (180 mcg) use RELEUKO single-dose vial.”

Instructions for Use for the Prefilled Syringe

A. Important Information
    1. Revise the important instructions to only include reference to the prefilled syringe and not the vial presentation. We recommend this revision since the Instructions for Use are for the prefilled syringe only.
    2. We recommend adding the following storage information to this section:

        Storing your prefilled syringe
        - Store the RELEUKO prefilled syringe in the refrigerator between 36˚F to 46˚F (2˚C to 8˚C).
        - **Do not freeze.**
        - Keep the RELEUKO prefilled syringe in the original carton to protect from light or physical damage.
        - Take the prefilled syringe out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.

- [redacted] (b) (4) **Throw away (dispose of) any RELEUKO prefilled syringe that has been left at room temperature for longer than 24 hours**.
- After you inject your dose, throw away (dispose of) any unused RELEUKO left in the prefilled syringe. **Do not** save unused RELEUKO in the prefilled syringe for later use.
- Keep RELEUKO and all medicines out of the reach of children.

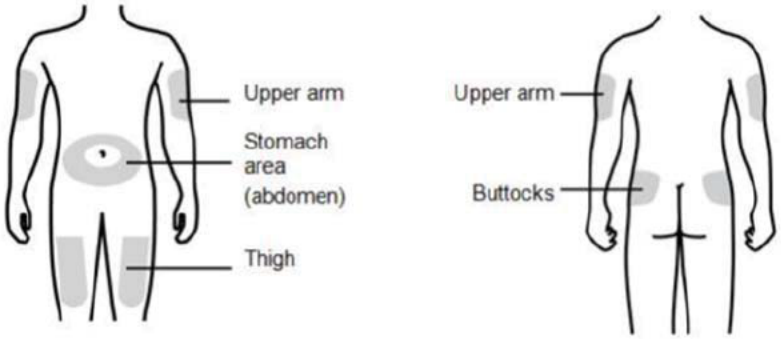
B. Identification of parts
   1. Revise the "[redacted] (b) (4) Label" to "[redacted] (b) (4) Label & expiration date".

C. What you need for your injection
   1. Include an image of and list adhesive bandage because users are instructed in Step 17 that they may cover the injection site with a small adhesive bandage, if needed.

D. Preparing to inject with the prefilled syringe

[redacted] (b) (4)

F. Step 7 Choose an injection site
   1. We note, in Figure G, the outer area of the upper arm is not labeled as an injection site on the front image. Revise the front image to include the injection site of outer upper arm.
   2. We recommend labeling the current Figure G with the appropriate injection sites to correspond with the text provided. For example:



G. Step 9 Remove the needle cap
    1. The image in Figure I, does not match the accompanying text of pulling of the needle cap straight off. As currently presented in the image, the needle cap is removed at an angle.

H. Step 14 Inject the dose
    1. (b) (4) We recommend revising this image to show the hand still pinching the skin.
    2. (b) (4)

I. Steps 16 and 17
    1. (b) (4)

Instructions for Use for the Vial

A. Important information
   1. Revise the important instructions to only include reference to the vial and not the prefilled syringe. We recommend this revision since the Instructions for Use are for the vial only.
   2. We recommend adding the following storage information to this section:

      Storing your RELEUKO vial
      - Store the vial in the refrigerator between 36˚F to 46˚F (2˚C to 8˚C).
      - **Do not freeze.**
      - Keep the vial in the original carton to protect from light or physical damage.
      - Take the vial out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
      - Throw away (dispose of) any vial that has been left at room temperature for longer than 24 hours.
      - After you inject your dose, throw away (dispose of) any unused RELEUKO left in the vial. **Do not** save unused RELEUKO in the vial for later use.

   3. In the Word document version of the IFU, the vial in Figure A is labeled as (b) (4). We recommend revising the vial label in Figure A to conditionally acceptable name, Releuko.
   4. In the Word document version of the IFU, delete the statement, (b) (4). We recommend this deletion as "cc" may be misinterpreted as "u" for units.[b]

B. What you need for your injection
   1. In Figure B, revise the label of the syringe to "Disposable Syringe". Additionally, label the parts of the disposable syringe including "needle cap", "syringe barrel with markings", and "plunger".
   2. In Figure B, include an image of an adhesive bandage as users are instructed in Step 24 that they may cover the injection site with a small adhesive bandage if needed.
   3. We recommend adding the following information about syringes and needles:

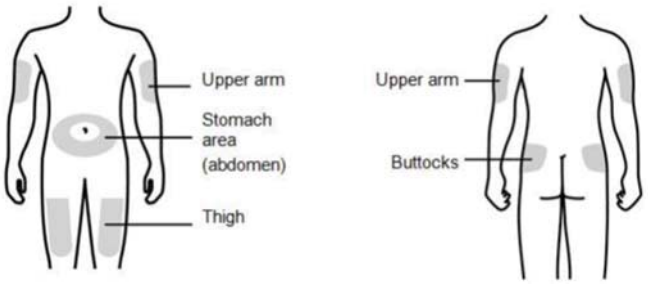
      - **Only use the disposable syringes and needles that your healthcare provider prescribes.**
      - **Only use the syringes and needles 1 time. Throw away (dispose of) any used syringes and needles. See STEP 23, for instructions about how to properly dispose of used syringes and needles.**
      - You should only use a syringe that is marked in tenths of milliliters (mL).

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 Feb 21]. Available at: www.ismp.org/tools/errorproneabbreviations.pdf.

- Your healthcare provider will show you how to measure the correct dose of RELEUKO. This dose will be measured in milliliters (mL).

C. Step 5 Allow to warm for 30 minutes
   1. In the Word document version of the IFU, place adequate space between the numerical strength and unit of measure (e.g. 300 mcg instead of 300mcg) to improve readability.
   2. Consider removing (b) (4) s currently presented, this may confuse the intended user.

D. Step 7 Chose an injection site
   1. We note, in Figure G, the outer area of the upper arm is not labeled as an injection site on the front image. Revise the front image to include the injection site of outer upper arm.
   2. We recommend labeling the current Figure G with the appropriate injection sites to correspond with the text provided. For example:



E. Step 12 Remove the needle cap
   1. We recommend adding a second bullet point that reads “Throw away the needle cap” as this instruction is not currently stated.
   2. The image in Figure I, does not match the accompanying text of pulling of the needle cap straight off. As currently presented in the image, the needle cap is removed at an angle.

F. Step 16 Check for air bubbles
   1. We recommend adding a Figure which corresponds with the text directing the user to “gently tap the side of the syringe to bring the bubbles to the top”. For example:

2. We recommend removing the text that states [redacted] (b) (4) as users have already been instructed to remove air bubbles and these statements may be confusing and misinterpreted.

G. Step 17 Check Dose
   1. We recommend revising the instructions to improve the clarity of the information presented. For example, revise to read "Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your healthcare provider."

H. Step 22 Remove the needle
   1. We recommend revising the instructions to improve the clarity of the information presented. For example, revise to read "When done, gently pull the needle out of the injection site at the same 45 to 90-degree angle used to insert it."

4.2 RECOMMENDATIONS FOR KASHIV BIOSCIENCES, LLC

We recommend the following be implemented prior to approval of this BLA:

A. All Container Labels and Carton Labeling

1. Revise the strength presentation '300 mcg/1.0 mL' to appear as '300 mcg/mL' in accordance with USP General Chapter <7>.

2. On the carton labeling, add the dosage form "Injection" to appear below the non-proprietary name as follows:

   Releuko
   (filgrastim-ayow)
   Injection

   If space permits, add the dosage form on the syringe and vial labels as well.

3. Include the dosage statement, "Dosage: See Prescribing Information" in accordance with 21 CFR 201.55.

4. As currently presented, the format of the expiration date is not indicated. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Vial label

1. To accurately reflect the correct package type term, revise "Single Use Vial" to read "Single-Dose Vial. Discard unused portion."

2. If space allows, we recommend adding the route of administration. For example, "For subcutaneous or intravenous use only".

3. Clarify the significance of the number located next to the lot number and expiration date (b) (4)). If it is an internal product code, we recommend removing and/or relocating this number to mitigate the potential for confusion due its proximity to the lot number and expiration date.

C. Syringe label

1. Include the unit of measure (mL) at the last syringe marking (e.g., 0.5 mL or 0.8 mL). We recommend this to mitigate the risk of dosing errors.

2. To accurately reflect the correct package type term, revise "Single Use Prefilled Syringe" to read "Single-Dose Prefilled Syringe." If space permits, add "Discard unused portion." immediately after.

3. If space allows, we recommend adding the route of administration. For example, "For subcutaneous use only"".

D. Vial carton labeling

1. Ensure that the strength is expressed as total protein content per total volume in the circle on Principal display panel (PDP). See USP General Chapters <7> Labeling. For example, revise the strength presentation to appear as 300 mcg/0.5 mL.

2. Include the statement "Discard unused portion." to appear after the package type term. To accommodate this change, relocate the statement "Sterile Solution- No Preservative" to the side panel. We recommend this to mitigate the risk of the vial being used to prepare more than one dose.

3. Revise "Single Use Vial" to read "Single-Dose Vial" to reflect the correct package type and relocate to below the route of administration on the principal display panel.

4. Please indicate where the required lot number and expiration date will appear as required per 21 CFR 610.60.

5. Revise and relocate the storage information, "**Store Refrigerated at 2° to 8°C (36° to 46°F).** Do not freeze. Do not shake." to the side panel.

6. Revise the net quantity statement to remove the "trailing zero" (i.e., 1.0). Revise to read "10 x 1 mL Single-dose Vials".

7. As currently presented, the inclusion of a product identifier is not indicated. In September 2018, FDA released draft guidance, which, when finalized will represent the agency's current thinking on the topics therein, on product identifiers required under the Drug Supply Chain Security Act.[c] The Act requires manufacturers and re-packagers, respectively, to affix or imprint a human-readable and machine-readable product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. Therefore, please confirm the inclusion and location of this information.

[c] Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

E. Syringe carton labeling ((b) (4) tray)

1. See D.1 through D.5 and revise labeling accordingly.

2. Per the Prescribing Information, the prefilled syringe should only be used for subcutaneous administration. As such, revise the route of administration statement to read “For subcutaneous use only.”

3. Revise “Read the full prescribing information before use” to read “Dosage: See Prescribing Information” in alignment with 21 CFR 201.55 to ensure consistency with all doses described in the prescribing information.

4. As currently presented, the inclusion and location of a linear barcode is not indicated. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label. Add the product’s linear barcode to each individual carton (tray) labeling in accordance with 21 CFR 201.25(c)(2).

F. Syringe carton labeling (outer carton)

1. See D.1 through D.7 and revise the carton labeling accordingly.

2. Per the Prescribing Information, the prefilled syringe should only be used for subcutaneous administration. As such, revise the route of administration statement to read “For subcutaneous use only.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Releuko that Kashiv submitted on February 2, 2021 and US-licensed Neupogen[d].

Table 2. Relevant Product Information for Releuko and US-licensed Neupogen

Product Name	Releuko	US-licensed Neupogen
Initial Approval Date	N/A	February 1991
Nonproprietary/Proper Name	filgrastim-ayow	filgrastim
Indication	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti- cancer drugs associated with a significant incidence of severe neutropenia with fever. • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). • Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti- cancer drugs associated with a significant incidence of severe neutropenia with fever. • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). • Reduce the incidence and duration of sequelae of severe neutropenia, (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

[d] Neupogen. Prescribing Information. Excerpted from Drugs at FDA. Cited 2021 APR 09. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103353s5197lbl.pdf

		• Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis • Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).
Route of Administration	Intravenous and subcutaneous	Intravenous and subcutaneous
Dosage Form	Injection	Injection
Strength	<u>Vials</u> • Injection: 300 mcg/mL in a single-use vial • Injection: 480 mcg/1.6 mL in a single-use vial <u>Prefilled Syringes</u> • Injection: 300 mcg/0.5 mL in a single-use prefilled syringe • Injection: 480 mcg/0.8 mL in a single-use prefilled syringe	<u>Vials</u> • Injection: 300 mcg/mL in a single-use vial • Injection: 480 mcg/1.6 mL in a single-use vial <u>Prefilled Syringes</u> • Injection: 300 mcg/0.5 mL in a single-use prefilled syringe • Injection: 480 mcg/0.8 mL in a single-use prefilled syringe
Dose and Frequency	• Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy: 5 mcg/kg/day once daily given as a subcutaneous injection, short intravenous infusion, or continuous intravenous infusion • Bone Marrow Transplantation: 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. • Congenital Neutropenia: 6 mcg/kg/day subcutaneous injection twice per day. • Idiopathic or Cyclic Neutropenia: 5 mcg/kg/day subcutaneous injection daily.	• Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy: 5 mcg/kg/day once daily given as a subcutaneous injection, short intravenous infusion, or continuous intravenous infusion • Bone Marrow Transplantation: 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. • Congenital Neutropenia: 6 mcg/kg/day subcutaneous injection twice per day. • Idiopathic or Cyclic Neutropenia: 5 mcg/kg/day subcutaneous injection daily. • Autologous Peripheral Blood Progenitor Cell Collection and Therapy: 10 mcg/kg/day given as a subcutaneous injection.

		Administer Neupogen for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. • Hematopoietic Syndrome of Acute Radiation Syndrome: 10 mcg/kg as a single daily subcutaneous injection.
How Supplied	RELEUKO injection is a clear, colorless, preservative-free solution supplied as: <u>Vials</u> • Single-dose vials containing 300 mcg/mL of filgrastim-ayow. Dispensing packs of 10 vials. • Single-dose vials containing 480 mcg/1.6 mL (300 mcg/mL) of filgrastim-ayow. Dispensing packs of 10 vials. <u>Prefilled Syringes</u> Single-dose, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe Plus™ Needle Guard, containing 300 mcg/0.5 mL of filgrastim-ayow. • Pack of 10 prefilled syringes Single-dose, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe Plus™ Needle Guard, containing 480 mcg/0.8 mL of filgrastim-ayow. • Pack of 10 prefilled syringes	NEUPOGEN injection is a clear, colorless, preservative-free solution supplied as: <u>Vials</u> • Single-dose vials containing 300 mcg/mL of filgrastim. Dispensing packs of 10 vials. • Single-dose vials containing 480 mcg/1.6 mL (300 mcg/mL) of filgrastim. Dispensing packs of 10 vials. <u>Prefilled Syringes</u> Single-dose, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe ® Needle Guard, containing 300 mcg/0.5 mL of filgrastim. • Pack of 1 prefilled syringe • Pack of 10 prefilled syringes Single-dose prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe ® Needle Guard, containing 480 mcg/0.8 mL of filgrastim. • Pack of 1 prefilled syringe • Pack of 10 prefilled syringes
Storage	Store Releuko at 2°C to 8°C (36°F to 46°F) in the pack to protect from light. Do not leave Releuko in direct sunlight. DO NOT freeze Releuko. Avoid shaking. Transport via a pneumatic has not been studied.	Store Neupogen at 2°C to 8°C (36°F to 46°F) in the carton to protect from light. Do not leave Neupogen in direct sunlight. Avoid freezing; if frozen thaw in the refrigerator before administration. Discard Neupogen if frozen more than once. Avoid shaking. Transport via a pneumatic has not been studied.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 9, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, “Releuko”, “filgrastim-ayow”, “BLA 761082” and “IND 115333”. Our search identified no previous labeling or human factors reviews.

APPENDIX C. HUMAN FACTORS: USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSIS

Use-Related Risk Analysis

- Submitted on July 10, 2017
  \\CDSESUB1\evsprod\bla761082\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\rpt-0887\human-factors-study-report.pdf

- Submitted on September 27, 2017
  \\CDSESUB1\evsprod\bla761082\0009\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\risk-analysis-report-dcp-0032.pdf

Comparative Analysis

- Submitted on January 5, 2018
  \\CDSESUB1\evsprod\bla761082\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neutropenia\5354-other-stud-rep\threshold-analysis-dcp-0044.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Releuko labels and labeling submitted by Kashiv BioSciences, LLC submitted on February 2, 2021.

- Container (vial) Labels
- Container (syringe) Labels
- Carton Labeling for Vials
- Carton Labeling for Syringes
- Prescribing Information (image not shown)
  \\CDSESUB1\evsprod\bla761082\0055\m1\us\114-labeling\draft-labeling\draft-label-text\draft-labeling-prescribing-info.pdf
- Instructions for Use – Vial (image not shown)
  \\CDSESUB1\evsprod\bla761082\0055\m1\us\114-labeling\draft-labeling\draft-label-text\draft-labeling-vial-ifu.pdf
- Instructions for Use – Syringe (image not shown)
  \\CDSESUB1\evsprod\bla761082\0055\m1\us\114-labeling\draft-labeling\draft-label-text\draft-labeling-syringe-ifu.pdf
- Prescribing Information, Patient Information, and Instructions for Use (image not shown)
  \\CDSESUB1\evsprod\bla761082\0055\m1\us\114-labeling\draft-labeling\draft-label-text\draft-labeling-prescribing-info-word.docx

G.2 Label and Labeling Images

Container Labels – Vial

(b) (4)

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

STEPHANIE L DEGRAW
06/07/2021 12:35:08 PM

HINA S MEHTA
06/07/2021 01:16:37 PM

LOLITA G WHITE
06/07/2021 01:41:17 PM

CHI-MING TU
06/07/2021 02:09:45 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	May 20, 2019
To:	Anne Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	RELEUKO (filgrastim-ayow)[1]
Dosage Form and Route:	injection, for subcutaneous or intravenous use
Application Type/Number:	BLA 761082
Applicant:	Kashiv BioSciences LLC

2

[1] The proprietary name RELEUKO and nonproprietary name filgrastim-ayow are conditionally acceptable until such time that the application is approved.

1 INTRODUCTION

On December 11, 2018, Adello Biologics LLC submitted for the Agency's review a class II resubmission of their original Biologics License Application (BLA) 761082 for RELEUKO (filgrastim-ayow), a proposed biosimilar to the Reference Product, NEUPOGN (filgrastim), in response to a Complete Response (CR) letter dated May 10, 2018. On February 19, 2019, Adello Biologics LLC notified FDA of the Change of Ownership and Transfer of Responsibilities for BLA 761082 to Kashiv BioSciences LLC. The proposed indications for RELEUKO (filgrastim-ayow) are as follows:

The proposed indications for RELEUKO are as follows:

- Patients with Cancer Receiving Myelosuppressive Chemotherapy: RELEUKO is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy: RELEKO is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia.
- Patients with Cancer Undergoing Bone Marrow Transplantation: RELEUKO is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.
- Patients with Severe Chronic Neutropenia: RELEUKO is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

On December 21, 2018, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for RELEUKO (filgrastim-ayow) injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for RELEUKO (filgrastim-ayow).

2 CONCLUSIONS

Due to outstanding deficiencies, DHP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON R MILLS
05/20/2019 02:08:04 PM

LASHAWN M GRIFFITHS
05/20/2019 02:37:34 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 29, 2019

To: Kris Kolibab, PhD, Senior Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Theragrastim (filgrastim-xxxx) for subcutaneous or intravenous use

BLA: 761082

This memo is in response to the Division of Hematology Products (DHP) labeling consult request dated December 21, 2018. Reference is made to a communication received by electronic mail on March 27, 2019 indicating that a Complete Response letter will be issued. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DHP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
04/29/2019 01:09:14 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 25, 2018

To: Kris Kolibab, PhD, Senior Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Theragrastim (filgrastim-xxxx) for subcutaneous or intravenous use

BLA: 761082

This memo is in response to Division of Hematology Products (DHP) labeling consult request dated August 10, 2017. Reference is made to a Complete Response letter that was issued on May 10, 2018. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DHP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
06/25/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	May 17, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFUs)
Drug Name (established name):	(b) (4) (theragrastim)
Dosage Form and Route:	Injection, for subcutaneous use
Application Type/Number:	BLA 761082
Applicant:	Adello Biologics

1 INTRODUCTION

On July 8, 2017, Adello Biologics submitted for the Agency's review a Biologics License Application (BLA) for (b) (4) (theragrastim) injection, for subcutaneous use, a proposed Biosimilar to reference product NEUPOGEN (filgrastim). On August 10, 2017, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI), Instructions for Use (IFUs) for (b) (4) (theragrastim) injection, for subcutaneous use.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFUs for (b) (4) (theragrastim) injection, for subcutaneous use.

2 CONCLUSIONS

Due to insufficient assurance of drug product sterility and inadequate qualification of the Theragrastim reference standard, DHP issued a Complete Response (CR) letter dated May 10, 2018. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHAWNA L HUTCHINS
05/17/2018