CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761212Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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:	November 26, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761212
Product Name, Dosage Form, and Strength:	Armlupeg (pegfilgrastim-unne)[a] injection, 6 mg/0.6 mL
Applicant Name:	Lupin Limited (Biotech Division) (Lupin)
FDA Received Date:	November 21, 2025 and November 25, 2025
TTT ID #:	2025-15006-2
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name suffix (pegfilgrastim-unne) was found conditionally acceptable on September 11, 2025.

1 PURPOSE OF MEMORANDUM

Lupin Limited (Biotech Division) (Lupin) submitted revised blister label and carton labeling received on November 21, 2025 and November 25, 2025 for Armlupeg. We reviewed the revised blister label and carton labeling submitted on November 25, 2025 for Armlupeg (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a recommendation that we made during a previous label and labeling review[b] and a recommendation from the Office of Pharmaceutical Quality (OPQ) to revise the quantity of sodium acetate anhydrous to 0.066 mg.

2 CONCLUSION

Lupin Limited (Biotech Division) (Lupin) implemented our recommendation and we have no additional recommendations at this time.

[b] Black, S. Review of Revised Label and Labeling for Armlupeg (BLA 761212). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 NOV 19. TTT ID: 2025-15006-1.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON NOVEMBER 25, 2025

Blister Label:

Carton Labeling:

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUE L BLACK
11/26/2025 08:58:29 AM

NICOLE F IVERSON
11/26/2025 09:18:47 AM

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)

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Date of This Review:	November 14, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761212
Product Name, Dosage Form, and Strength:	Armlupeg (pegfilgrastim-unne)[a] injection, 6 mg/0.6 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Lupin Limited (Biotech Division) (Lupin)
FDA Received Date:	May 30, 2025 and September 11, 2025
TTT ID #:	2025-15006
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name suffix (pegfilgrastim-unne) was found conditionally acceptable on September 11, 2025.

1 INTRODUCTION

As part of the approval process for Armlupeg (pegfilgrastim-unne) injection, we reviewed the proposed Armlupeg Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label, blister label and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Armlupeg (pegfilgrastim-unne) is a proposed 351(k) biosimilar and the US-licensed Reference Product (RP) is Neulasta (pegfilgrastim), BLA 125031.

1.2 REGULATORY HISTORY

On November 4, 2016[b] and November 15, 2019[c] (written response) BPD Type 2 meetings were held with the Sponsor. During the meetings the Agency recommended that the Sponsor submit a comprehensive use-related risk analysis (URRA) for the proposed product to determine the necessity of a human factor (HF) validation study.

DMEPA evaluated the use-related risk analysis, physical comparison, and IFU comparison of LUBT004 with US-licensed Neulasta submitted under IND 131463 on July 28, 2020[d]. The review concluded that a HF validation study did not need to be submitted for Agency review for the proposed single-dose prefilled syringe (PFS) at the time.

Lupin Limited (Biotech Division) previously submitted BLA 761212 on April 2, 2021. We completed a label and labeling review on September 10, 2021[e]. Our container label and carton labeling recommendations were provided to Lupin Limited on October 12, 2021. However, the applicated received a Complete Response letter on February 1, 2024 due to issues with product quality and facility inspections.[f]

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[b] Memorandum of Meeting Minutes for Lupin pegfilgrastim (IND 131463). Silver Spring (MD): FDA, CDER, OHOP, DHP (US); 2016 NOV 04. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8040ee79.

[c] Memorandum of Written Response for LUBT004 (IND 131463). Silver Spring (MD): FDA, CDER, OHOP, DHP (US); 2019 NOV 15. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8052861f.

[d] DeGraw, S. Human Factors: Use-Related Risk Analysis Review for LUBT004* (pegfilgrastim-xxxx). IND 131463. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 28. RCM No.: 2020-999. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8058235b.

[e] Karpow, C. Label and Labeling Review for "LUBT004" Armlupeg (pegfilgrastim-xxxx). BLA 761212. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 10. OSE RCM: 2021-682. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061b087.

[f] Thompson, C on behalf of Ann Farrell. Complete Response for BLA 761212. Silver Spring (MD): FDA, CDER, OND, Division of Non-Malignant Hematology (DNH) (US); 2024 FEB 01. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8072200d.

Lupin Limited (Biotech Division) submitted a Class 2 Resubmission on May 14, 2024.[g] We completed a label and labeling review and memo on September 12, 2024[h] and September 26, 2024[i] respectively. However, the applicated received a Complete Response letter on November 14, 2024 due to facility inspection issues.[j]

Thus, Lupin Limited (Biotech Division) submitted a Class 2 Resubmission on May 30, 2025.[k]

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

During the review of this application, the Division of Non-Malignant Hematology (DNH) and Office of Therapeutic Biologics and Biosimilars (OTBB) discussed that with the recent approval of a vial presentation for US-licensed Neulasta in pediatric patients weighing less than 45 kg, the Prescribing Information states that the PFS should be used for adult patients of any weight and pediatric patients weighing 45 kg and greater[l]. As Armlupeg is only proposed as a PFS, the team concluded (b) (4) should be removed. In addition, the team concluded that Section 2.3 should contain a statement to clearly state there is no presentation for Armlupeg that allows

[g] Resubmission (BLA 761212 Pegfilgrastim). Pune (India): Lupin Limited (Biotech Division); 2024 MAY 14. Available from: \\CDSESUB1\EVSPROD\bla761212\0041\m1\us\cover-letter.pdf.

[h] Topper, C. Label and Labeling Review for "LUBT004" Armlupeg (pegfilgrastim-unne). BLA 761212. Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 SEP 12. OSE RCM: 2024-9492. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8076a7f9.

[i] Topper, C. Label and Labeling Review for "LUBT004" Armlupeg (pegfilgrastim-unne). BLA 761212. Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 SEP 26. OSE RCM: 2024-9492-1. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8077044b.

[j] Thompson, C on behalf of Ann Farrell. Complete Response for BLA 761212. Silver Spring (MD): FDA, CDER, OND, Division of Non-Malignant Hematology (DNH) (US); 2024 NOV 14. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8077fe06.

k Cover Letter (BLA 761212 and Armlupeg). Pune (India): Lupin Limited (Biotech Division); 2025 MAY 30. Available from: \\CDSESUB1\EVSPROD\bla761212\0054\m1\us\cover-letter.pdf.

[l] Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. AUG 2025. [cited 2025 OCT 23]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125031Orig1s209lbl.pdf.

weight-based dosing for pediatric patients below 45 kg. We agree with this approach from a medication error perspective.

4 CONCLUSION

The proposed Armlupeg Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label, blister label and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Non-Malignant Hematology (DNH) in Section 5 and for Lupin Limited (Biotech Division) in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. Section 2 Dosage and Administration

a. As currently presented, the room temperature range is presented with the range in Fahrenheit followed by the range in Centigrade, which is inconsistent with the presentation of the temperature range in Section 16 *How Supplied/Storage and Handling*. For consistency within the PI, we recommend presenting the temperature range in Centigrade first, followed by the equivalent temperature range in Fahrenheit [i.e., 20°C to 25°C (68°F to 77°F)].

b. As currently presented, Section 2.3 *Preparation and Administration* does not directly state that there is no presentation of Armlupeg for pediatrics weighing less than 45 kg. This may lead to dosing and administration errors. In concurrence with DNH and OTBB, we recommend including clear information regarding the lack of a presentation of Armlupeg for pediatrics weighing less than 45 kg and revising Section 2.3 *Preparation and Administration* as follows:

> Prefilled Syringe for Manual Use
> For adult patients of any weight and pediatric patients weighing 45 kg and greater, the single-dose prefilled syringe for manual use is intended for subcutaneous administration of a single 6 mg/0.6 mL dose of Armlupeg. The syringe does not bear graduation marks and therefore does not allow for direct administration of doses less than 6 mg/0.6 mL. There is no presentation for Armlupeg that allows weight-based dosing for pediatric patients below 45 kg.

c. As currently presented in Section 2.1 *Patients with Cancer Receiving Myelosuppressive Chemotherapy*, the statement [redacted (b) (4)] chemotherapy" is not consistent with current labeling terminology. We recommend removing [redacted (b) (4)] to be consistent with the current labeling terminology.

d. As currently presented in Section 2.3 *Preparation and Administration*, the word [redacted] in the statement "Discard any [redacted] prefilled syringe left at room temperature for greater than 48 hours." may imply [redacted] we recommend removing [redacted] from this statement.

2. Section 16 How Supplied/Storage and Handling

a. As currently presented, the carton is described as [redacted] for the PFS. For consistency within Section 16, we recommend revising [redacted] to "carton".

B. Patient Package Insert (PPI)

1. As currently presented in *How should I store Armlupeg single-dose prefilled syringes* section, the word [redacted] in the statement [redacted] we recommend removing [redacted] from this statement.

C. Instructions for Use (IFU)

1. As currently presented in *Storing the prefilled syringe* section, the room temperature range is not stated in the storage statement, "Take the prefilled syringe out of the refrigerator 30 minutes before use and allow it to reach room temperature…". Improperly storing this product could lead to deteriorated drug medication errors. We recommend including the temperature range in this storage statement.

2. As currently presented, the statement [redacted] This information may cause confusion as to how the product is supplied. We recommend removing the statement [redacted]

3. As currently presented, figure numbers are not consistently referenced in the corresponding written descriptions of the step. For consistency, we recommend including the figure numbers (see examples below in parenthesis) in the corresponding written descriptions of the step.

a. Inspect the medicine and prefilled syringe (See Figure 4).
b. Select and clean the injection site (See Figures 6 and 7).
c. Clean the injection site with an alcohol swab (See Figure 7). Let the skin dry.

d. Hold the prefilled syringe by the syringe [redacted] (b) (4) Carefully pull the gray needle cap straight off and away from the body. (See Figure 8)
e. Pinch the injection site to create a firm surface (See Figure 9).
f. Hold the pinch. Insert the needle into the skin at 45 to 90 degrees. (See Figure 10)

4. As currently presented, Figure 8 depicts multiple written descriptions of steps (i.e., pulling the needle cap straight off, throwing away the needle cap and air bubble removal). This may lead to confusion which image refers to which step. For clarity, we recommend revising step E as follows:

E. Hold the prefilled syringe by the syringe body. Carefully pull the gray needle cap straight off and away from the body. (See Figure 8)

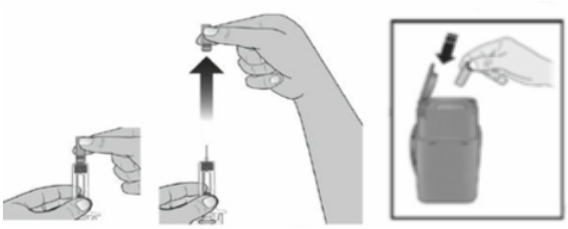

Figure 8

- Do not remove the gray needle cap from the prefilled syringe until you are ready to inject.
- Do not twist or bend the needle cap.
- Do not hold the prefilled syringe by the plunger rod
- Do not put the gray needle cap back onto the syringe or never recap. If the needle cap is removed accidently and you are not ready for the injection, discard (throw away) the opened syringe and use a new syringe when ready.

Important: Throw the gray needle cap into the sharps disposal container (See Figure XX).

Figure XX

5. As currently presented, the statement [redacted] (b) (4) may be improved for clarity. We recommend creating a new step "F" and providing more specific instructions for air bubble removal as follows. In addition, adjust future step letters and figure numbers.

F. Point the needle up and gently tap the syringe body with your fingers until the air bubble rises to the top of the syringe (See Figure x).

Figure x

6. As currently presented, Figure 12 is presented above the written description of the step, which is inconsistent with other figures in the IFU which appear below written descriptions of the step. For consistency within the IFU, we recommend relocating Figure 12 below the written description "While the needle is still inserted in the skin, slowly move your thumb back, allowing the plunger rod to rise. This will release the needle safety guard to safely cover the needle. Then remove the syringe from the injection site. (See Figure x)."

6 RECOMMENDATIONS FOR LUPIN LIMITED (BIOTECH DIVISION)

A. General Comments (Container Label and Carton Labeling)

1. As currently presented, the format for the expiration date is MM/YYYY. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or 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 forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

2. The placement of the graphic as part of the first letter "A" in the proprietary name is prominent. Placement of the graphic as part of the first letter in the proprietary name competes with readability of the proprietary name, which may lead to misinterpretation of the proprietary name as "Carmlupeg". We continue to recommend moving or decreasing the prominence of the graphic as part of the proprietary name as it may lead to misinterpretation of the proprietary name.

B. Container Label

1. As currently presented, the presentation of the route of administration on the container label (i.e., For subcutaneous use only) is inconsistent with the presentation of the route of administration on the blister label and carton labeling (i.e., For Subcutaneous Use Only). For consistency within the labels and labeling, we recommend presenting the route of administration on the container label as "For Subcutaneous Use Only".

2. Clarify if the linear barcode is oriented in a vertical position on the syringe. Barcodes placed in a horizontal position may not scan due to container curvature. The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode.

C. Blister Label and Carton Labeling

1. As currently presented, the storage statement does not state to store in the original carton, which is inconsistent with the PI. This may lead to deteriorated drug errors. For consistency with the PI, we recommend revising the storage statement to "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake."

2. As currently presented, the proper name and the dosage form on the blister label and carton labeling are separated by multiple spaces whereas the proper name and dosage form on the container label is separated by one space. For consistency within the labels and labeling, we recommend using one space between the proper name and the dosage form [i.e., (pegfilgrastim-unne) Injection] on the blister label and carton labeling.

D. Carton Labeling

1. As currently presented, the National Drug Code (NDC) is not included in the product identifier. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. Include the NDC number in the product identifier. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)."

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for the US-licensed Reference Product (RP) and Armlupeg received on September 11, 2025 from Lupin Limited (Biotech Division).

Table 2. Relevant Product Information for the US-licensed Reference Product (RP) and Armlupeg.

Product Name	Neulasta[m] (BLA 125031)	Armlupeg
Initial Approval Date	January 31, 2002	N/A
Nonproprietary Name	pegfilgrastim	pegfilgrastim-unne
Indication	Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. • Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).
Dosage Form	Injection	injection
Strength	6 mg/0.6 mL	6 mg/0.6 mL
Route of Administration	subcutaneous	subcutaneous

[m] Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2025 AUG 18. [cited 2025 SEP 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125031Orig1s209lbl.pdf.

Table 2. Relevant Product Information for the US-licensed Reference Product (RP) and Armlupeg.		
Product Name	Neulasta[m] (BLA 125031)	Armlupeg
Dose and Frequency	Patients with cancer receiving myelosuppressive chemotherapy • For adult patients of any weight and pediatric patients weighing 45 kg and greater, the recommended dosage is 6 mg subcutaneously once per chemotherapy cycle. • For pediatric patients weighing less than 45 kg, use weight-based dosing; refer to Table 1 • Do not administer between 14 days before and 24 hours after administration of chemotherapy. Patients acutely exposed to myelosuppressive doses of radiation • For adults of any weight and pediatric patients weighing 45 kg and greater, the recommended dosage is two doses, 6 mg each, subcutaneously one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after. • For pediatric patients weighing less than 45 kg, use weight-based dosing; refer to Table 1	Patients with cancer receiving myelosuppressive chemotherapy • For adult patients of any weight and pediatric patients weighing 45 kg and greater, the recommended dosage is 6 mg subcutaneously once per chemotherapy cycle. (b) (4) • Do not administer between 14 days before and 24 hours after administration of chemotherapy. Patients acutely exposed to myelosuppressive doses of radiation • For adults of any weight and pediatric patients weighing 45 kg and greater, the recommended dosage is two doses, 6 mg each, subcutaneously one week apart. Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after. (b) (4)

Table 2. Relevant Product Information for the US-licensed Reference Product (RP) and Armlupeg.

Product Name	Neulasta[m] (BLA 125031)	Armlupeg
	Table 1. Dosing of Neulasta for Pediatric Patients Weighing Less Than 45 kg **Body Weight** / **Neulasta Dose** / **Volume to Administer** Less than 10 kg* / See below* / See below* 10 kg to 20 kg / 1.5 mg / 0.15 mL 21 kg to 30 kg / 2.5 mg / 0.25 mL 31 kg to 44 kg / 4 mg / 0.4 mL * For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta.	

Table 2. Relevant Product Information for the US-licensed Reference Product (RP) and Armlupeg.		
Product Name	Neulasta[m] (BLA 125031)	Armlupeg
How Supplied	<u>Neulasta single-dose prefilled syringe for manual use</u> Neulasta injection is a clear, colorless solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard. The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex). Neulasta is provided in a carton containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 55513-190-01). Neulasta prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. <u>Neulasta Onpro® kit</u> Neulasta Onpro kit is provided in a carton containing one sterile prefilled syringe and one sterile on-body injector (OBI) for Neulasta (NDC 55513-192-01). The Neulasta injection single-dose prefilled syringe contains 0.64 mL of a clear, colorless solution that delivers 6 mg/0.6	Armlupeg (pegfilgrastim-unne) injection is a clear, colorless solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim-unne, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Plus PassiveTM Needle Guard. The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex). Armlupeg is provided in a (b) (4) containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 70748-273-01). Armlupeg prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. (b) (4)

Table 2. Relevant Product Information for the US-licensed Reference Product (RP) and Armlupeg.		
Product Name	Neulasta[m] (BLA 125031)	Armlupeg
	mL of pegfilgrastim when used with the OBI for Neulasta. The prefilled syringe is supplied with a 27-gauge, 1/2-inch needle. The syringe does not bear graduation marks and is only to be used with the OBI for Neulasta. The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex). <u>Neulasta single-dose vial</u> Neulasta injection is a clear, colorless, solution, supplied in a single-dose vial containing 4 mg pegfilgrastim. Neulasta is provided in a carton containing one 4 mg/0.4 mL single-dose vial (NDC 55513-099-01).	

Table 2. Relevant Product Information for the US-licensed Reference Product (RP) and Armlupeg.		
Product Name	Neulasta[m] (BLA 125031)	Armlupeg
Storage	<u>Neulasta single-dose prefilled syringe for manual use</u> Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once. <u>Neulasta Onpro® kit</u> Store Neulasta Onpro kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until 30 minutes prior to use. Because the OBI for Neulasta is at room temperature during the period of use, Neulasta Onpro kit should not be held at room temperature longer than 12 hours prior to use. Discard Neulasta Onpro kit if stored at room temperature for more than 12 hours. Do not freeze the kit. Keep in the carton until use to protect from light. Do not shake the prefilled syringe. Do not use the OBI for Neulasta if its packaging has been previously opened. <u>Neulasta single-dose vial</u>	Store refrigerated between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

Table 2. Relevant Product Information for the US-licensed Reference Product (RP) and Armlupeg.		
Product Name	Neulasta[m] (BLA 125031)	Armlupeg
	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Do not freeze. Discard unused vials stored at room temperature for more than 48 hours.	
Container Closure	Not provided	Not provided

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[n] along with postmarket medication error data, we reviewed the following Armlupeg labels and labeling submitted by Lupin Limited (Biotech Division).

- Prescribing Information received on September 11, 2025, available from \\CDSESUB1\EVSPROD\bla761212\0056\m1\us\bla-761212-uspi-tc.docx
- Patient Package Insert received on September 11, 2025, available from \\CDSESUB1\EVSPROD\bla761212\0056\m1\us\bla-761212-ppi-tc.docx
- Instructions for Use received on May 30, 2025, available from \\CDSESUB1\EVSPROD\bla761212\0054\m1\us\bla-761212-ifu-0046.docx
- Container label received on May 30, 2025
- Blister label received on May 30, 2025
- Carton labeling received on May 30, 2025

B.2 Container Label, Blister Label and Carton Labeling Images

Container Label

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

Blister label

Carton Labeling:

APPENDIX C. PREVIOUS DMEPA REVIEWS

On September 15, 2025, we searched for previous DMEPA reviews relevant to this current review using the term, "pegfilgrastim". Our search identified numerous previous reviews (refer to Table 3), and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. List of Previous DMEPA Reviews for pegfilgrastim products

Application #	Product name	Applicant	Strength	Approval Date	Previous DMEPA Reviews
BLA 125031	Neulasta (pegfilgrastim) Injection	Amgen	6 mg/0.6 mL	January 31, 2002	2025-15028-3 2025-15028-2 2025-15028-1 2025-15028
BLA 761075	Fulphila (pegfilgrastim-jmdb)	Biocon Biologics Inc.	6 mg/0.6 mL	June 04, 2018	2024-12196 2023-4623-1 2023-4623
BLA 761084	Fylnetra (pegfilgrastim-pbbk)	Kashiv Biosciences LLC	6 mg/0.6 mL	May 26, 2022	2025-13448
BLA 761111	Nyvepria (pegfilgrastim-apgf)	Hospira Inc.	6 mg/0.6 mL	June 10, 2020	2019-1274-1 2019-1274
BLA 761173	Stimufend (pegfilgrastim-fpgk)	Fresenius Kabi USA	6 mg/0.6 mL	September 1, 2022	2025-15696-2 2025-15696-1 2025-15696
BLA 761039	Udenyca (pegfilgrastim-cbqv)	Coherus Biosciences, Inc.	6 mg/0.6 mL	November 2, 2018	2023-6816
BLA 761045	Ziextenzo (pegfilgrastim-bmez)	Sandoz Inc	6 mg/0.6 mL	November 4, 2019	2022-1083
BLA 761212	Armlupeg (pegfilgrastim-unne)	Lupin Limited (Biotech Division)	6 mg/0.6 mL	Subject of this review	2024-9492-1 2024-9492

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/s/

SUE L BLACK
11/14/2025 04:17:09 PM

NICOLE F IVERSON
11/17/2025 06:53:22 AM

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:	November 5, 2025
To:	Carleveva Thompson, MS Senior Regulatory Project Manager **Division of Nonmalignant Hematology**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Melissa Khashei, 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):	[LUBT004] ARMLUPEG (pegfilgrastim-unne)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761212
Applicant:	Lupin Limited, India c/o Lupin Pharmaceuticals, Inc.

[1] LUBT004 is a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proposed proprietary name ARMLUPEG and nonprorietary name -unne were found to be conditionally acceptable on August 18, 2025 and August 6, 2024, respectively, by the Division of Medication Error Prevention and Analysis I (DMEPA 1).

1 INTRODUCTION

On May 30, 2025, Lupin Limited, India c/o Lupin Pharmaceuticals, Inc. resubmitted for the Agency's review an original Biologics License Application (BLA) 761212 for [LUBT004] ARMLUPEG (pegfilgrastim-unne) injection, a proposed biosimilar to US-licensed NEULASTA (pegfilgrastim) injection (BLA 125031). This resubmission is in response to the Agency's Complete Response (CR) letter dated November 14, 2024. With this submission, the Applicant proposes the following indications for ARMLUPEG (pegfilgrastim-unne) injection:

- to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
- to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

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 June 18, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ARMLUPEG (pegfilgrastim-unne) injection.

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

2 MATERIAL REVIEWED

- Draft [LUBT004] ARMLUPEG (pegfilgrastim-unne) injection PPI received on May 30, 2025, revised throughout the review cycle, and received by DMPP and OPDP on October 28, 2025.
- Draft [LUBT004] ARMLUPEG (pegfilgrastim-unne) injection prefilled syringe IFU received on May 30, 2025, revised throughout the review cycle, and received by DMPP and OPDP on October 28, 2025.
- Draft [LUBT004] ARMLUPEG (pegfilgrastim-unne) injection Prescribing Information (PI) received on May 30, 2025, revised throughout the review cycle, and received by DMPP on October 28, 2025.
- Approved US-licensed NEULASTA (pegfilgrastim) injection labeling dated August 18, 2025.

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 IFU, 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 PPI using Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- evaluated the PPI and IFU per the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- evaluated the IFU per the criteria as specified in the Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the PPI and IFU are consistent with the approved labeling for US-licensed NEULASTA (pegfilgrastim) injection where applicable

4 CONCLUSIONS

The PPI and IFU 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 PPI and IFU 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 PPI and IFU.

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
11/05/2025 06:56:30 AM

MELISSA KHASHEI
11/05/2025 07:20:17 AM

BARBARA A FULLER
11/05/2025 07:32:24 AM

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

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

Memorandum

Date: November 4, 2025

To: Carleveva Thompson, Senior Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, Associate Director for Labeling, DNH

From: Melissa Khashei, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for ARMLUPEG® (pegfilgrastim-unne) injection, for subcutaneous use

BLA: 761212

Background:
In response to DNH's consult request dated June 18, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for ARMLUPEG® (pegfilgrastim-unne) injection, for subcutaneous use.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 28, 2025, and we do not have any comments at this time.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on May 30, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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/s/

MELISSA KHASHEI
11/04/2025 02:49:14 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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:	November 19, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761212
Product Name, Dosage Form, and Strength:	Armlupeg (pegfilgrastim-unne)[a] injection, 6 mg/0.6 mL
Applicant Name:	Lupin Limited (Biotech Division) (Lupin)
FDA Received Date:	November 17, 2025
TTT ID #:	2025-15006-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] The nonproprietary name suffix (pegfilgrastim-unne) was found conditionally acceptable on September 11, 2025.

1 PURPOSE OF MEMORANDUM

Lupin Limited (Biotech Division) (Lupin) submitted revised container label, blister label and carton labeling received on November 17, 2025 for Armlupeg. We reviewed the revised container label, blister label and carton labeling for Armlupeg (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 CONCLUSION

Lupin Limited (Biotech Division) (Lupin) implemented all of our recommendations. Lupin confirmed the expiration date will be presented as "YYYY-MM" in numerical format. In addition, Lupin confirmed the linear barcode is oriented in a vertical position on the syringe and does not impact barcode scanning.

The container label is acceptable from a medication error perspective. However, the blister label and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Lupin Limited (Biotech Division) (Lupin) in Section 3.

3 RECOMMENDATIONS FOR LUPIN LIMITED (BIOTECH DIVISION) (LUPIN)

A. General Comments (Blister Label and Carton Labeling)

1. As currently presented, the storage statement is inconsistent between the labels and labeling:

    - Blister label and carton labeling: Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.
    - Prescribing Information (PI): Store refrigerated between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

    For consistency with the PI, we recommend revising the storage statement to:

    - Blister label and carton labeling: Store refrigerated between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.

[b] Black, S. Label and Labeling Review for Armlupeg (BLA 761212). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 NOV 14. TTT ID: 2025-15006.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON NOVEMBER 17, 2025

Container Label:

Blister Label:

Carton Labeling:

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/s/

SUE L BLACK
11/19/2025 04:37:43 PM

NICOLE F IVERSON
11/20/2025 09:21:38 AM

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:	November 5, 2024
To:	Carleveva Thompson, MS Senior Regulatory Project Manager **Division of Nonmalignant Hematology**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Melissa Khashei, 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):	[LUBT004] ARMLUPEG (pegfilgrastim-unne)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761212
Applicant:	Lupin Limited, India c/o Lupin Pharmaceuticals, Inc.

[1] LUBT004 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proposed proprietary name ARMLUPEG was found to be conditionally acceptable on August 9, 2024, and the proposed nonprorietary name -unne was found to be conditionally acceptable on August 6, 2024, by the Division of Medication Error Prevention and Analysis I (DMEPA 1).

1 INTRODUCTION

On May 14, 2024, Lupin Limited, India c/o Lupin Pharmaceuticals, Inc. resubmitted for the Agency's review an original Biologics License Application (BLA) 761212 for [LUBT004] ARMLUPEG (pegfilgrastim-unne) injection, a proposed biosimilar to US-licensed NEULASTA (pegfilgrastim) injection (BLA 125031). This resubmission is in response to the Agency's Complete Response (CR) letter dated February 1, 2024. With this submission, the Applicant proposes the following indications for ARMLUPEG (pegfilgrastim-xxx) injection:

- to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
- to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

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 June 11, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ARMLUPEG (pegfilgrastim-unne) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 13, 2024.

2 MATERIAL REVIEWED

- Draft [LUBT004] ARMLUPEG (pegfilgrastim-unne) injection PPI received on May 14, 2024, revised throughout the review cycle, and received by DMPP and OPDP on September 25, 2024.
- Draft [LUBT004] ARMLUPEG (pegfilgrastim-unne) injection prefilled syringe IFU received on June 18, 2024, revised throughout the review cycle, and received by DMPP and OPDP on September 25, 2024.
- Draft [LUBT004] ARMLUPEG (pegfilgrastim-unne) injection Prescribing Information (PI) received on May 14, 2024, revised throughout the review cycle, and received by DMPP on September 25, 2024.
- Approved US-licensed NEULASTA (pegfilgrastim) injection labeling dated as follows: PI dated February 2, 2021, and single-dose prefilled syringe PPI dated January 5, 2021 and IFU dated April 28, 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 IFU, 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 using Arial font, size 12.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- evaluated the PPI per the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- evaluated the IFU per the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the PPI and IFU are consistent with the approved labeling for US-licensed NEULASTA (pegfilgrastim) injection where applicable

4 CONCLUSIONS

The PPI and IFU 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 PPI and IFU 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 PPI and IFU.

Please let us know if you have any questions.

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LAURIE J BUONACCORSI
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MELISSA KHASHEI
11/05/2024 11:11:36 AM

LASHAWN M GRIFFITHS
11/05/2024 11:27:40 AM

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

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

Memorandum

Date: October 3, 2024

To: Carleveva Thompson, Senior Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, Associate Director for Labeling, DNH

From: Melissa Khashei, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for ARMLUPEG® (pegfilgrastim-unne) injection, for subcutaneous use

BLA: 761212

Background:
In response to DNH's consult request dated June 11, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for ARMLUPEG® (pegfilgrastim-unne) injection, for subcutaneous use.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 25, 2024, and we do not have any comments at this time.

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

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on September 18, 2024 and October 1, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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/s/

MELISSA KHASHEI
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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:	September 26, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761212
Product Name, Dosage Form, and Strength:	"LUBT004"[a] Armlupeg[b] (pegfilgrastim-unne)[c] Injection, 6 mg/0.6 mL
Applicant Name:	Lupin Limited (Biotech Division)
FDA Received Date:	September 18, 2024
TTT ID #:	2024-9492
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] LUBT004 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim).

[b] The proposed proprietary name, Armlupeg, was found conditionally acceptable on August 9, 2024.

[c] The nonproprietary name, pegfilgrastim-unne, was found conditionally acceptable on August 6, 2024.

1 PURPOSE OF MEMORANDUM

Lupin Limited (Biotech Division) submitted revised container label, blister label and carton labeling received on September 18, 2024 for Armlupeg (pegfilgrastim-unne). We reviewed the revised container label, blister label and carton labeling for Armlupeg (pegfilgrastim-unne) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[d]

2 CONCLUSION

Lupin Limited (Biotech Division) implemented all of our recommendations and we have no additional recommendations at this time.

[d] Topper, C. Label and Labeling Review for "LUBT004" (BLA 761212). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 SEP 12. TTT ID: 2024-9492.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON SEPTEMBER 18, 2024

Container Label

Carton Labeling

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/s/

CHRISTINA A TOPPER
09/26/2024 10:43:10 AM

NICOLE F IVERSON
09/26/2024 11:42:18 AM

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)

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Date of This Review:	September 12, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761212
Product Name, Dosage Form, and Strength:	"LUBT004"[a] Armlupeg[b] (pegfilgrastim-unne)[c] Injection, 6 mg/0.6 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Lupin Limited (Biotech Division)
FDA Received Date:	May 14, 2024, June 11, 2024 and June 18, 2024
TTT ID #:	2024-9492
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

[a] LUBT004 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim).

[b] The proposed proprietary name, Armlupeg, was found conditionally acceptable on August 9, 2024.

[c] The nonproprietary name, pegfilgrastim-unne, was found conditionally acceptable on August 6, 2024

1 INTRODUCTION

As part of the approval process for Armlupeg (pegfilgrastim-unne) Injection, we reviewed the proposed Armlupeg Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label, blister label and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Armlupeg (pegfilgrastim-unne) is a proposed 351(k) biosimilar and the US-licensed Reference Product (RP) is Neulasta (pegfilgrastim), BLA 125031, which was approved on January 31, 2002.

1.2 REGULATORY HISTORY

On November 4, 2016[d] and November 15, 2019[e] (written response) BPD Type 2 meetings were held with the Sponsor. During the meetings the Agency recommended that the Sponsor submit a comprehensive use-related risk analysis (URRA) for the proposed product to determine the necessity of a human factor (HF) validation study.

DMEPA evaluated the use-related risk analysis, physical comparison, and IFU comparison of LUBT004 with US-licensed Neulasta submitted under IND 131463 on July 28, 2020[f]. The review concluded that a HF validation study did not need to be submitted for Agency review for the proposed single-dose prefilled syringe at the time.

Lupin Limited (Biotech Division) previously submitted BLA 761212 on April 2, 2021. We completed a label and labeling review on September 10, 2021[g]. Our container label and carton labeling recommendations were provided to Lupin Limited on October 12, 2021. However, the applicated received a Complete Response letter on February 1, 2024 due to issues with product quality and facility inspections.[h]

Thus, Lupin Limited (Biotech Division) submitted a Class 2 Resubmission on May 14, 2024.[i]

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[d] Memorandum of Meeting Minutes for Lupin pegfilgrastim (IND 131463). Silver Spring (MD): FDA, CDER, OHOP, DHP (US); 2016 NOV 04. https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8040ee79

[e] Memorandum of Written Response for LUBT004 (IND 131463). Silver Spring (MD): FDA, CDER, OHOP, DHP (US); 2019 NOV 15. https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8052861f

[f] DeGraw, S. Human Factors: Use-Related Risk Analysis Review for LUBT004* (pegfilgrastim-xxxx). IND 131463. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 28. RCM No.: 2020-999.

[g] Karpow, C. Label and Labeling Review for "LUBT004" Armlupeg (pegfilgrastim-xxxx). BLA 761212. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 10. OSE RCM: 2021-682.

[h] Thompson, C on behalf of Ann Farrell. Complete Response for BLA 761212. Silver Spring (MD): FDA, CDER, OND, Division of Non-Malignant Hematology (DNH) (US); 2024 FEB 01.

[i] Resubmission (BLA 761212 Pegfilgrastim). Pune (India): Lupin Limited (Biotech Division); 2024 MAY 14. Available from: \\CDSESUB1\EVSPROD\bla761212\0041\m1\us\cover-letter.pdf.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761212.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

The proposed Armlupeg Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label, blister label and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Non-Malignant Hematology (DNH) in Section 4 and for Lupin Limited (Biotech Division) in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. Section 3 Dosage Forms and Strengths

   a. The statement "Injection: 6 mg/0.6 mL in a single-dose prefilled syringe for manual use only." is presented without a bullet, which may reduce readability. We recommend adding a bullet in front of the statement to improve readability and to be consistent with US-licensed Neulasta.

B. Patient Package Insert (PPI)

1. As currently presented, the last bullet under the "How Should I Store Armlupeg" section includes the word (b) (4) following "hours", which is conflicting on the appropriate room temperature storage. We recommend revising the last bullet to remove the word (b) (4) to avoid confusion.

C. Instructions for Use (IFU)

1. As currently presented, the statement under Step 2, (b) (4) lacks clarity on the medication administration sites. This may lead to administration and wrong technique errors. We recommend revising the statement from (b) (4) to "Select and clean the injection site." to avoid confusion and administration errors.

5 RECOMMENDATIONS FOR LUPIN LIMITED (BIOTECH DIVISION)

A. General Comments (Container Label(s) and Carton Labeling)

1. The placement of the graphic as part of the first letter "A" in the proprietary name is prominent. Placement of the graphic as part of the first letter in the proprietary name competes with readability of the proprietary name, which may lead to misinterpretation of the proprietary name as "Carmlupeg". We continue to recommend moving or decreasing the prominence of the graphic as part of the proprietary name as it may lead to misinterpretation of the proprietary name.
2. As currently presented, the manufacturer name, "LUPIN" competes in prominence with other critical information on the principal display panel (PDP). The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. As, the manufacturer information is present on the label; we recommend removing the duplicate name "LUPIN" on the PDP to reduce clutter and improve readability of other critical information.
3. As currently presented, the format for the expiration date is not clearly defined. Clarify whether "MM" is intended to indicate a 2-letter abbreviation (e.g., JU) for the month or 2-digit (e.g., 01). 2-letter abbreviations have led to confusion for the months of March vs. May and June vs. July.
4. The "Rx only" statement appears more prominent than other critical information (e.g., route of administration, cautionary statement) on the principal display panel. The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel. We recommend the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

B. Container Label

1. The route of administration is not present on the principal display panel. Failure to include the route of administration on the principal display panel may lead to wrong route errors. Add the route of administration "For subcutaneous use only" in accordance with 21 CFR 201.100(b)(3).

C. Blister Label

1. The net quantity statement is in close proximity to the product strength on the PDP. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing. We recommend relocating the net quantity statement away from and less prominent than the product strength,

such as to the bottom of the PDP. See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*

D. Blister Label and Carton Labeling

1. Relocate the route of administration statement to appear directly underneath the product strength as follows:

    Armlupeg
    (pegfilgrastim-unne) Injection
    6 mg/0.6 mL
    For Subcutaneous Use Only

2. As currently presented, the net quantity statement can be improved. We recommend revising the net quantity statement by spelling out the net quantity from "1 x 0.6 mL single dose prefilled syringe" to "One 0.6 mL Single-Dose Prefilled Syringe" for additional clarity.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Armlupeg received on May 14, 2024 from Lupin Limited (Biotech Division), and the US-licensed Reference Product (RP).

Table 2. Relevant Product Information for Armlupeg and the US-licensed Reference Product (RP).

Product Name	Armlupeg	Neulasta[j] (BLA 125031)
Initial Approval Date	N/A	January 31, 2002
Nonproprietary Name	pegfilgrastim-unne	pegfilgrastim
Indication	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia • Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). Limitations of Use Armlupeg is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.	• To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Limitations of Use Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. • To increase survival in patients acutely exposed to myelosuppressive doses of radiation
Dosage Form	Injection	Injection
Strength	6 mg/0.6 mL	6 mg/0.6 mL
Route of Administration	subcutaneous	subcutaneous

[j] Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. February 2021. [cited 2024 AUG 06]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125031s203lbl.pdf.

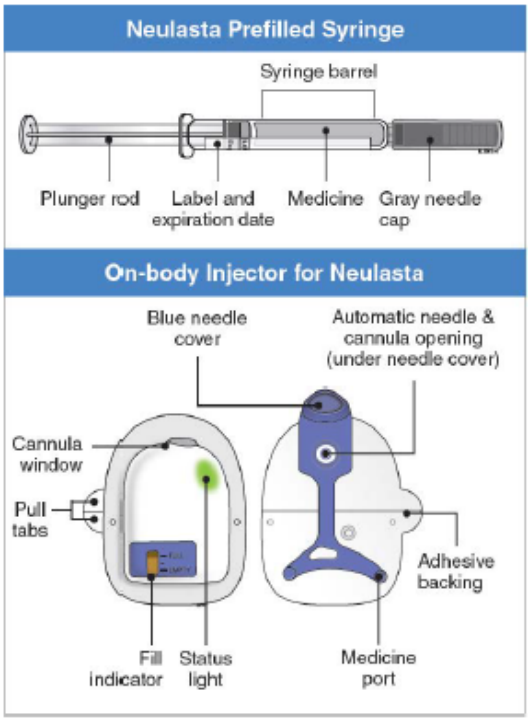
<table>
<tr><th colspan="3">Table 2. Relevant Product Information for Armlupeg and the US-licensed Reference Product (RP).</th></tr>
<tr><td>Product Name</td><td>Armlupeg</td><td>Neulasta[j] (BLA 125031)</td></tr>
<tr><td>Dose and Frequency</td><td>Patients with Cancer Receiving Myelosuppressive Chemotherapy
The recommended dosage of Armlupeg is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. (b) (4) Do not administer Armlupeg between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome
The recommended dose of Armlupeg is two doses, 6 mg each, administered subcutaneously one week apart. (b) (4) Administer the first dose as soon as possible after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose.
(b) (4)</td><td>Patients with cancer receiving myelosuppressive chemotherapy
The recommended dosage of Neulasta is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Do not administer Neulasta between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome
The recommended dose of Neulasta is two doses, 6 mg each, administered subcutaneously one week apart. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Administer the first dose as soon as possible
after suspected or confirmed exposure to radiation levels greater than 2 gray (Gy). Administer the second dose one week after the first dose.
Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg
<table>
<tr><th>Body Weight</th><th>Neulasta Dose</th><th>Volume to Administer</th></tr>
<tr><td>Less than 10 kg*</td><td>See below*</td><td>See below*</td></tr>
<tr><td>10 - 20 kg</td><td>1.5 mg</td><td>0.15 mL</td></tr>
<tr><td>21 - 30 kg</td><td>2.5 mg</td><td>0.25 mL</td></tr>
<tr><td>31 - 44 kg</td><td>4 mg</td><td>0.4 mL</td></tr>
</table>
*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta.</td></tr>
</table>

Table 2. Relevant Product Information for Armlupeg and the US-licensed Reference Product (RP).		
Product Name	Armlupeg	Neulasta[j] (BLA 125031)
How Supplied	Armlupeg (pegfilgrastim-unne) injection is a clear, colorless solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pefilgrastim-unne, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Plus Passive™ Needle Guard. The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex). Armlupeg is provided in a (b) (4) containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 70748-273-01). Armlupeg prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. (b) (4)	Neulasta single-dose prefilled syringe for manual use Neulasta injection is a clear, colorless solution supplied in a prefilled single-dose syringe for manual use containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard. The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex). Neulasta is provided in a (b) (4) containing one sterile 6 mg/0.6 mL prefilled syringe (NDC 55513-190-01). Neulasta prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (6 mg/0.6 mL) for direct administration. Use of the prefilled syringe is not recommended for direct administration for pediatric patients weighing less than 45 kg who require doses that are less than the full contents of the syringe. Neulasta Onpro® kit Neulasta Onpro kit is provided in a carton containing one sterile prefilled syringe and one sterile on-body injector (OBI) for Neulasta (NDC 55513-192-01). The Neulasta injection single-dose prefilled syringe contains 0.64 mL of a clear, colorless solution that delivers 6 mg/0.6 mL of pegfilgrastim when used with the OBI for Neulasta. The prefilled syringe is supplied with a 27-gauge, 1/2-inch needle. The syringe does not bear

Table 2. Relevant Product Information for Armlupeg and the US-licensed Reference Product (RP).		
Product Name	Armlupeg	Neulasta[j] (BLA 125031)
		graduation marks and is only to be used with the OBI for Neulasta. The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex).
Storage	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.	Neulasta single-dose prefilled syringe Store refrigerated between 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once. Neulasta Onpro® kit Store Neulasta Onpro kit in the refrigerator at 36°F to 46°F (2°C to 8°C) until 30 minutes prior to use. Because the OBI for Neulasta is at room temperature during the period of use, Neulasta Onpro kit should not be held at room temperature longer than 12 hours prior to use. Discard Neulasta Onpro kit if stored at room temperature for more than 12 hours. Do not use the OBI for Neulasta if its packaging has been previously opened.

Table 2. Relevant Product Information for Armlupeg and the US-licensed Reference Product (RP).		
Product Name	Armlupeg	Neulasta[j] (BLA 125031)
Container Closure	The primary packaging components of Lupin Pegfilgrastim injection are Type (b) (4) glass syringe with a 27G ½ inch fixed injection needle, a rigid needle shield and (b) (4) rubber stopper (manufactured by (b) (4) Lupin Pegfilgrastim 6 mg/0.6 mL for subcutaneous use, is a solution for injection presented in pre-filled syringe (Type (b) (4) glass) with a 27 G ½ inch fixed injection needle and a rigid needle shield, (b) (4) plunger stopper and (b) (4) Ultrasafe® plus passive needle safety guard.	

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Armlupeg labels and labeling submitted by Lupin Limited (Biotech Division).

- Prescribing Information received on May 14, 2024, available from \\CDSESUB1\EVSPROD\bla761212\0041\m1\us\bla-761212-uspi-clean.pdf
- Patient Package Insert received on May 14, 2024, available from \\CDSESUB1\EVSPROD\bla761212\0041\m1\us\bla-761212-ppi-clean.pdf
- Instructions for Use received on June 18, 2024, available from \\CDSESUB1\EVSPROD\bla761212\0046\m1\us\bla-761212-ifu-0046.pdf
- Container label(s) received on June 11, 2024
- Carton labeling received on June 11, 2024
- Blister label received on June 11, 2024

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

B.2 Container Label(s) and Carton Labeling Images

Carton labeling

APPENDIX C. PREVIOUS DMEPA REVIEWS

On August 6, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, 'pegfilgrastim'. Our search identified numerous previous reviews (refer to table 3), and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. List of Previous DMEPA Reviews for pegfilgrastim products

Application #	Product name	Applicant	Strength	Status	Previous DMEPA Reviews
BLA 125031	Neulasta (pegfilgrastim) Injection	Amgen	6 mg/0.6 mL	Approved January 31, 2002	2015-1012 2017-2626 2019-511
BLA 761075	Fulphila (pegfilgrastim-jmdb)	Biocon Biologics Inc.	6 mg/0.6 mL	Approved June 04, 2018	2017-2463 2023-4623 2023-4623-1
BLA 761039	Udenyca (pegfilgrastim-cbqv)	Coherus Biosciences, Inc.	6 mg/0.6 mL	Approved November 02, 2018	2018-920 2018-920-1 2019-1979 2020-14
BLA 761212	Armlupeg (pegfilgrastim-unne) Injection	Lupin Limited (Biotech Division)	6 mg/0.6 mL	Subject of this review	2021-682

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/s/

CHRISTINA A TOPPER
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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 26, 2022
To:	Carleveva Thompson, MS Regulatory Project Manager **Division of Nonmalignant Hematology**
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 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):	"LUBT 004" ARMLUPEG (pegfilgrastim-xxxx)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761212
Applicant:	Lupin Limited c/o Lupin Pharmaceuticals, Inc.

[1] LUBT 004 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proprietary name ARMLUPEG was found to be conditionally acceptable on July 1, 2021. The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder, "pegfilgrastim-xxxx" is used throughout this review to refer to the nonproprietary name for this product until approved.

1 INTRODUCTION

On April 2, 2021, Lupin Limited c/o Lupin Pharmaceuticals, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761212 for ARMLUPEG (pegfilgrastim-xxxx) injection, a proposed biosimilar to US-licensed NEULASTA (pegfilgrastim) injection (BLA 125031). The Applicant proposes the following indication for ARMLUPEG (pegfilgrastim-xxx) injection: to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile 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 May 25, 2021 and May 21, 2021, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ARMLUPEG (pegfilgrastim-xxxx) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 10, 2021.

2 MATERIAL REVIEWED

- Draft ARMLUPEG (pegfilgrastim-xxxx) injection PPI received on April 2, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 18, 2021.
- Draft ARMLUPEG (pegfilgrastim-xxxx) injection Prescribing Information (PI) received on April 2, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on November 18, 2021.
- Approved US-licensed NEULASTA (pegfilgrastim) injection labeling dated as follows: PI dated February 2, 2021 and single-dose prefilled syringe 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, size 10

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)

4 CONCLUSIONS

- The PPI is acceptable with our recommended changes.
- Agency plans to request that the Applicant more closely align their IFU with U.S. licensed -NEULASTA (pegfilgrastim) injection, single-dose prefilled syringe IFU. We defer review of the ARMLUPEG (pegfilgrastim-xxxx) injection, single-dose prefilled syringe IFU at this time. We will complete a collaborative review of the Applicant's revised single-dose prefilled syringe IFU after it has 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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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 15, 2021

TO: Ann T. Farrell, MD
Director
Division of Nonmalignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
(DGDSI)
(OSIS)

SUBJECT: Remote record review (RRR) of Lupin Bioresearch Center, Pune, Maharashtra, India

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the analytical portion of study LBC-19-146 (BLA 761212, pegfilgrastim) conducted at Lupin Bioresearch Center, Pune, Maharashtra, India. An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

I observed the following objectionable conditions during the RRR: Lupin rejected study runs and performed repeat analysis of study samples without proper justification, and contradictory to their established acceptance criteria. Lupin also reported extrapolated data outside the valid concentration range in a method validation run.

1.1. Recommendation

Based on the outcome of the RRR and based on the responses provided by Lupin demonstrating the firm’s corrective and preventative actions, the objectionable conditions had no impact on the integrity of the data or subject safety. Therefore, I conclude the amended data from the audited study are reliable.

2. Reviewed Studies

Study LBC-19-146 (BLA 761212)
"A Double-Blind, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Two-Period Crossover Comparative Pharmacokinetics-Pharmacodynamics (PK-PD) Study of Lupin's Pegfilgrastim 6mg/0.6mL subcutaneous injection manufactured by Lupin Limited, India and Neulasta® (Pegfilgrastim 6mg/0.6mL) subcutaneous injection manufactured by Amgen Inc. US administered in Healthy, Adult, Human Subjects"
Sample Analysis Period: 02/20/2020 – 07/02/2020

3. Scope of RRR

OSIS scientist Kara A. Scheibner, Ph.D., reviewed the analytical portion of the above study conducted at Lupin Bioresearch Center, Pune, Maharashtra, India from 09/13/2021 to 09/17/2021. The RRR included an examination of Lupin's facility, computer systems and software, equipment, SOPs, method validation MV-20-007, and study sample analysis. It also included virtual Zoomgov.com interviews with Lupin's management and staff. This was OSIS' first audit of a large molecule method at Lupin, and thus, the RRR specifically focused on the firm's large molecule operations.

4. RRR Observations

At the conclusion of the RRR, I observed objectionable conditions, and discussed the following items with the firm's management during the RRR close-out meeting.

My evaluation of the observations that were discussed, and the firm's response dated 10/07/2021 (**Attachment 1**) are presented below.

4.1. Observations discussed at the close-out of RRR

4.1.1. Observation 1: The firm rejected study runs in study LBC-19-146 without proper justification. Specifically, runs 200220_P01, 200220_P02, 220220_P11, and 220220_P12 met all established acceptance criteria, but were rejected as "trial runs" used to optimize sample dilutions.

4.1.2. Observation 2: The firm performed repeat analysis of study samples from study LBC-19-146 without proper justification and reported data from the repeat analyses as the final sample

concentration. The following samples yielded valid, reportable concentrations obtained in runs 200220_P01, 200220_P02, 220220_P11, and 220220_P12, that were inappropriately rejected:

Run	Study Sample ID	Run	Study Sample ID	Run	Study Sample ID	Run	Study Sample ID
20220_P01	(b) (6)	20220_P02	(b) (6)	220220_P11	(b) (6)	220220_P12	(b) (6)

Firm's Response (Observations 1 and 2): Lupin responded jointly to observations 1 and 2, and the firm acknowledged both observations. Lupin explained that runs 200220_P01 and 200220_P02 were indeed both acceptable but were rejected due to the large number of samples from subject (b) (6) with concentrations above the ULOQ. Lupi t they used samples from subject (b) (6) to assess (b) (4) dilution factors in runs 220220_P11, 220220_P12, and 220220_P13, as a 1:8 dilution factor was insufficient to yield sample concentrations in the validated range. However, they acknowledged that rejection of runs 200220_P01, 200220_P02, 220220_P11, and 220220_P12 was not justified, and that results for samples with valid concentrations from these runs should have been reported.

As a corrective action, Lupin reevaluated runs 200220_P01, 200220_P02, 220220_P11, and 220220_P12 and accepted results from all samples from these runs with valid concentrations for subjects (b) (6) and (b) (6) The firm submitted the revised data with this response (**Attachments 2 and 3**). Lupin also performed pharmacokinetic (PK) and statistical analyses on the study data using the revised concentrations (in conjunction with revised concentrations from **observation 3; Attachment 4**). There was no impact on the study outcome.

In addition to these corrective actions, Lupin also reviewed and revised SOP LBC-BR091-02 – Study Sample Analysis of Large Molecules (**Attachment 5**). The revised SOP states that study runs meeting acceptance criteria must be accepted; that valid, acceptable concentrations will be reported; and that study samples will not be used for assay optimization.

OSIS Evaluation (Observations 1 and 2): Lupin's response is acceptable. All corrective actions taken were appropriate, and there were no impacts on the study outcome. Furthermore, the firm's preventative measures will likely ensure that these observations do not affect future large molecule studies.

4.1.3 Observation 3: The firm did not treat calibration standards, QCs and study samples consistently in MV-20-007 and study LBC-19-146. Specifically, calibration standards and QC samples with one duplicate value outside the calibration range and one duplicate value within the calibration range were considered valid results if the %CV was acceptable and the mean concentration was within acceptable %bias. However, study samples with one duplicate value outside the calibration range and one duplicate value within the calibration range with an acceptable %CV were considered invalid, and those samples were repeated.

Firm's Response: Lupin acknowledged the observation. They explained that they based repeat analysis code "H" on the non-reportable value guidelines outlined in the ICH M10, and repeated any samples with one replicate value above the ULOQ or below the LLOQ, regardless of %CV values.

As a corrective action, Lupin identified 131 samples repeated under code H that yielded a mean value within the valid calibration range and an acceptable %CV, and subsequently reverted the results to the original concentration values (**Attachment 6**). Lupin also performed PK and statistical analyses on the revised data in conjunction with the revised sample concentrations from subjects (b) (6) and (b) (6) described above (**Attachment 1**). The revised sample analysis report is included herein as **Attachment 7**.

Lupin also modified SOP LBC-BR091-02 to make code H obsolete.

OSIS Evaluation: Lupin's corrective and preventative actions were acceptable. As noted above, the revised sample concentrations from observations 1, 2, and 3 did not impact the study outcome.

4.1.4. Observation 4: The firm reported extrapolated data values for QCs with nominal concentrations outside the calibration range in method validation MV-20-007. Specifically, back-calculated LQ (nominal concentrations of (b) (4) respectively) were reported from cali n 310120_P05V2. This run was truncated due to masking of unacceptable calibration standards 08 and 09; this resulted in a revised LLOQ concentration of 1800 pg/mL.

Firm's Response: Lupin acknowledged the observation. They stated that the LQC and LLOQ values should have been reported as non-reportable (NR) due to the truncated calibration curve. Lupin revised section 8.1 of the method validation report to clarify that the calibration curve did not meet acceptance criteria, and that LQC and LLOQ concentrations were out of range (**Attachment 8**). The results of the LQC and LLOQ samples were changed to NR. Table 12.0 was also revised to reflect the failing calibration curve.

Lupin reviewed and revised SOP LBC-BR093-02 – Method Validation for Biologics using Ligand Binding Assay to support Pharmacokinetics/Pharmacodynamics studies (**Attachment 9**). The revision clarified acceptance criteria for the calibration curve, specifically regarding failure of two consecutive calibration standards.

OSIS Evaluation: Lupin's corrective and preventative actions were acceptable. There was no impact on the outcome of the method validation.

Draft: KAS 12/14/2021
Edit: MFS 12/14/2021; KAB 12/14/2021

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/s/

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MICHAEL F SKELLY
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KIMBERLY A BENSON
12/15/2021 10:34:05 AM

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

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

Memorandum

Date: November 23, 2021

To: Carleveva Thompson, MS, 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 ARMLUPEG® (pegfilgrastim-xxxx) injection, for subcutaneous use

BLA: 761212

In response to DNH's consult request dated May 21, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for ARMLUPEG® (pegfilgrastim-xxxx) injection, for subcutaneous use (Armlupeg).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Carleveva Thompson) on November 17, 2021, and we have no additional comments at this time.

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 October 25, 2021, and we do not have any comments.

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

15 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

REBECCA A FALTER
11/23/2021 10:29:39 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	10/27/2021		
To:	Hamet Toure		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	Choose an item.
From	Dunya Karimi OPEQ/OHT3/DHT3C		
Through (Team)	Injection Devices Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	ICCR: 82779 ICC: 2100413 Submission: BLA 761212 Sponsor: Lupin Limited Drug/Biologic: Pegfilgrastim-xxxx Indications for Use: Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs, associated with a clinically significant incidence of febrile neutropenia		
Recommendation	**Final Recommendation:** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies		
	Comments to Review Team:		
	PMC/PMR or CR Deficiencies:		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. PURPOSE

This review provides an assessment of the needle safety device constituent part[1] of the prefilled syringe product.

This review will cover the following review areas:

☒ Needle safety device constituent performance [1]
☒ Needle safety Stability
☒ Needle safety Control strategy

CDRH Quality Systems Assessment / Facilities consult not required per internal MAP 5017.7

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[2]) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

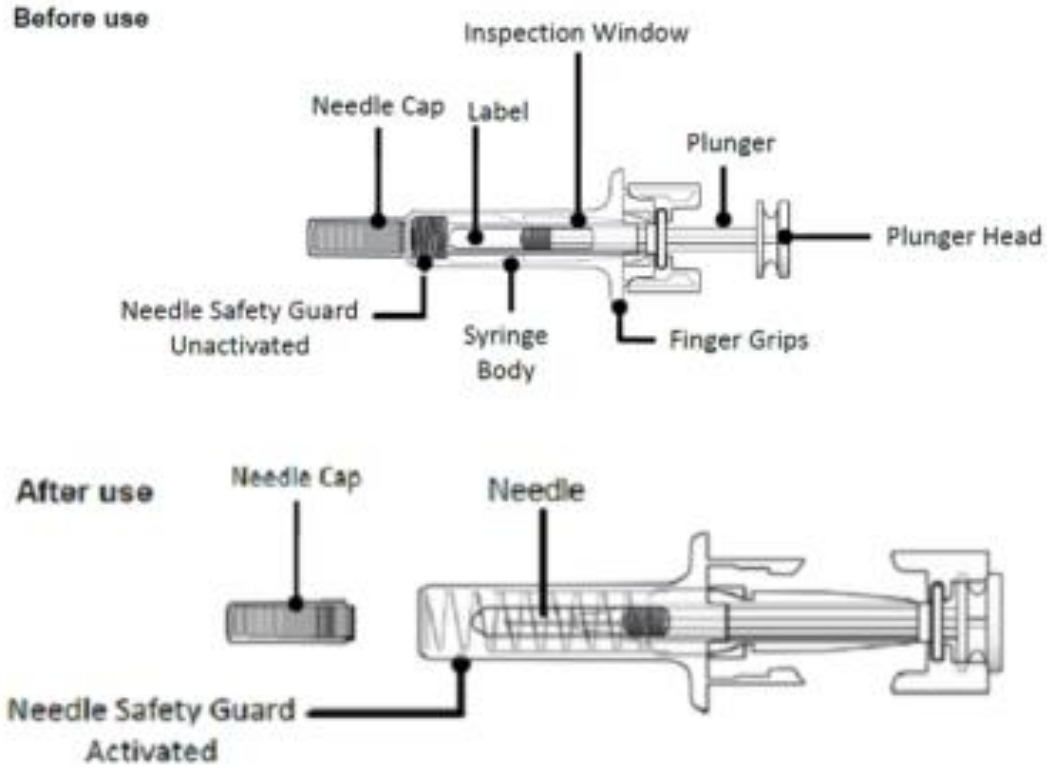

Figure 1 Pictorial Presentation of Lupin Pegfilgrastim Pre-filled Syringe

[1] The scope of this review will be limited to the device constituent performance in accordance with ISO 23908:2011 Sharps Injury Protection and FDA guidance Medical Devices with Sharps Injury Prevention Features. Therefore, for a PFS with a needle safety device constituent the review will be limited to needle safety performance requirements will not cover functions of the primary container (breakloose force, glide force, needle shield removal force, etc.,).

[2] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Health Care Professional
Injection Site	Subcutaneous
Needle safety type (active or passive)	Active
Delivered Dose Volume	6mg/0.6mL
Shelf-life/Storage, including excursions (e.g., 36months, 5C)	36 months

3. DEVICE PERFORMANCE REVIEW

3.1. Design Verification & Validation

Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Shelf-life (Y/N)	Shipping/ Transportation (Y/N)	Drop/Free Fall Testing (Y/N)
Needle Safety Activation force	(b) (4)	*n= 510,* (b) (4)	Clinical data – users are caregivers, spec is within benchmark - acceptable	(b) (4)	Y, ASTM 4169	ISO 11608-5 in the carton , n=30 devices per drop orientation (vertical A, Vertical B, Horizontal), 1m free fall
Needle Safety Activation Force – Shipping *<<if the preconditioning has a separate acceptance criteria/report, create a new row and name the preconditioning >>*	Visual	N=150, Y	N/A	N/A	Y, ASTM 4169	N/A
Needle safety lockout force/override force/safe mode challenge	(b) (4) Force required to override the activated locked guard from locked activated position to the un-activated position	n=510, (b) (4)	Clinical data and Anthropometric data used, Y	(b) (4)	Y, ASTM 4169	ISO 11608-5 in the carton , n=30 devices per drop orientation (vertical A, Vertical B, Horizontal), 1m free fall
Needle Safety Pre-activation	No pre-activation of needle safety feature – visual inspection	n=150, Y	n/a	(b) (4)	Y, ASTM 4169	ISO 11608-5 in the carton , n=30 devices per drop orientation

						(vertical A, Vertical B, Horizontal), 1m free fall
Needle safety Access in safe mode	After completion of injection safety shield should completely cover opening f needle and needle tip should not be accessible.	A (b) (4) tube mimicking a finger tip does not contact the extremity of the needle point when positioned against the safety shield	(b) (4) (mimicking a fingertip), is positioned against the safety shield of the device.	*N/A*	*N/A*	*N/A*

Reviewer Comments:
Needle safety features were all verified and validated appropriately. Adequate samples sizes were used where applicable, shelf-life, shipping/transportation, and drop/free fall testing was all conducted per the appropriate standards.

4. CONTROL STRATEGY REVIEW

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Needle safety activation	Needle safety functional features are only evaluated as EPRs if they impact the device's ability to deliver the dose. The Needle safety feature for this device is only activated after injection is complete and does not impact the devices ability to deliver the dose.	N/A

<<END OF REVIEW>>

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/s/

HAMET M TOURE
11/03/2021 09:42:45 AM

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:	September 10, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761212
Product Name, Dosage Form, and Strength:	"LUBT004"[a] Armlupeg (pegfilgrastim-xxxx)[b] injection, 6.0 mg/0.6 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Lupin Limited (Biotech Division)
FDA Received Date:	April 2, 2021 and May 24, 2021
OSE RCM #:	2021-682
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

[a] LUBT004 has been developed as a proposed biosimilar to US-licensed Neulasta (pegfilgrastim). The proposed proprietary name for this BLA, Armlupeg, was found conditionally acceptable on June 22, 2021.

[b] The nonproprietary name suffix for this BLA has not yet been determined; therefore, the placeholder, pegfilgrastim-xxxx, is used throughout this review to refer to the nonproprietary name and suffix for this product.

1 REASON FOR REVIEW

Under the 351(k) application pathway, Lupin Limited (Biotech Division) submitted BLA 761212 for Armlupeg (pegfilgrastim-xxxx) injection for Agency review as a proposed biosimilar to US-licensed Neulasta. This review evaluates the proposed Armlupeg container label, carton labeling, Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors.

1.1 PRODUCT BACKGROUND

US-licensed Neulasta (pegfilgrastim) was approved on January 31, 2002 under BLA 125031. Armlupeg is being proposed for the indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Like US-licensed Neulasta, the proposed strength is a 6 mg/0.6 mL in a single-dose, ungraduated prefilled syringe with a passive needle guard.

1.2 REGULATORY HISTORY

On November 4, 2016[c] and November 15, 2019[d] (written response) BPD Type 2 meetings were held with the Sponsor. During the meetings the Agency recommended that the Sponsor submit a comprehensive use-related risk analysis (URRA) for the proposed product to determine the necessity of a human factor (HF) validation study.

DMEPA evaluated the use-related risk analysis, physical comparison, and IFU comparison of LUBT004 with US-licensed Neulasta submitted under IND 131463 on July 28, 2020[e]. The review concluded that an HF validation study did not need to be submitted for Agency review for the proposed single-dose prefilled syringe at the time.

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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

[c] Memorandum of Meeting Minutes for Lupin pegfilgrastim (IND 131463). Silver Spring (MD): FDA, CDER, OHOP, DHP (US); 2016 NOV 04. https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8040ee79

[d] Memorandum of Written Response for LUBT004 (IND 131463). Silver Spring (MD): FDA, CDER, OHOP, DHP (US); 2019 NOV 15. https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8052861f

[e] DeGraw, S. Human Factors: Use-Related Risk Analysis Review for LUBT004* (pegfilgrastim-xxxx). IND 131463. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 28. RCM No.: 2020-999.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F
Pediatric Considerations	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 Prescribing Information (PI), Patient Information (PPI), Instructions for Use (IFU), container label, and carton labeling for Armlupeg to identify deficiencies that may lead to medication errors and other areas of improvement.

The proposed PI, PPI, IFU, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. For the Division, we note that the PI lacks clarity on the recommended (b) (4) and repetitive information in the storage instructions. In addition, the Patient Information contains formatting mistakes and the Instructions for Use can be revised for clarity on storage and format of the images/text. For the Applicant, we note the labels and labeling lack clarity in the strength, storage statement, and format of expiration date. We also note lack of clarity on the readability of the container label, a graphic as part of the proprietary name, prominence of the Rx only statement, and inconsistency in the terminology used for the recommended dosage. These factors may confuse the user and inadvertently lead to medication errors. We provide our recommendations for the Division in Section 4.1 and for Lupin in Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Armlupeg PI, IFU, PPI, container label, and carton labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations for Division of Non-Malignant Hematology in Section 4.1 and recommendations for Lupin in Section 4.2 below. We advise they be implemented prior to approval of BLA 761212.

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

A. Prescribing Information

1. Highlights of Prescribing Information

(b) (4)

2. Dosage and Administration Section

a. (b) (4)

3. How Supplied/Storage and Handling Section

a. We recommend removing the first statement as this is repetitive and not needed in this section. In addition, we recommend you consider including the proper name in the first sentence of the How Supplied/Storage and Handling Section.

4. Patient Counseling Information

a. As currently displayed, "Acute Respiratory Distress Syndrome" is included as part of the first bullet. We recommend you move "Acute Respiratory Distress Syndrome" to its own bullet.

5. Patient Information

a. We recommend you remove the line separating Capillary Leak Syndrome and the bullets of symptoms.

b. We recommend you correct the bullet and indentation for "Myelodysplastic syndrome and acute myeloid leukemia."

6. Instructions for Use – General Issues

a. The headings and subheadings are redundant. We recommend you consider removing redundant statements in headings and subheadings where appropriate.

7. Instructions for Use

a. The fifth bullet under the storage and handling section states "room temperature" but the temperature is not defined. We recommend adding the temperature degrees, i.e. 68°F to 77°F (20°C to 25°C).

b. We recommend you bold both words, “Do not” under the heading, “Using the prefilled syringe” for consistency.

c. As currently presented, the “Using the prefilled syringe” does not include a statement to not used the prefilled syringe if the needle guard has been activated. We recommend adding the following statement to the “Using the prefilled syringe” section:

   “The prefilled syringe has a needle guard that automatically activates to cover the needle after the injection is given. Do not use a prefilled syringe if the needle guard has been activated. Use another prefilled syringe that has not been activated and is ready to use.”

d. The language used in bullet 2A can be improved for reader comprehension. For example, we recommend you consider, “Place the sealed tray containing the prefilled syringe on a clean, well-lit surface, at room temperature for 30 minutes before you give an injection.”

e. We recommend the image containing the supplies that need to be gathered be placed below the step and list of the supplies for ease or readability.

f. “Do not” is not bolded in section 3. We are concerned this negative statement might be overlooked. We recommend you bold “Do not” in number 3.B.

g. We note all the images pertaining to individual steps are located above the written description of the step. We recommend placing the pictures next to or below the written text.

4.2 RECOMMENDATIONS FOR LUPIN LIMITED (BIOTECH DIVISION)

A. General Comments (Carton labeling and container labels)

1. The placement of the graphic as part of the first letter “A” in the proprietary name is prominent. Placement of the graphic as part of the first letter in the proprietary name competes with readability of the proprietary name, which may lead to misinterpretation of the proprietary name as “Carmlupeg”. We recommend moving or decreasing the prominence of the graphic as part of the proprietary name as it may lead to misinterpretation of the proprietary name.
2. The proprietary name is printed in different colors. Specifically, the ‘lu’ is printed in (b) (4) whereas the rest of the proprietary name is printed in (b) (4). We are concerned this might detract from the readability of the proprietary name. We recommend you consider presenting the proprietary name in one color.
3. We recommend de-bolding the “Rx Only” statement as this information appears with equal prominence to critical information on the principal display panel.

4. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read "Dosage: See prescribing information."
5. A refrigeration statement is absent. We are concerned this is important information to minimize the risk of the wrong storage medication errors. In addition, some letters are inappropriately capitalized. We recommend you revise the storage statement to read,

   "Store refrigerated [redacted] (b) (4) 2°C to 8°C (36°F to 46°F).
   Do not freeze or shake.
   Protect from light."

6. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends 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-MM-DD format if only numerical characters are used or 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. Carton labeling
1. The strength is not presented below the proper name and dosage form. The product strength is critically important information for the end user. We recommend you add the strength per total volume to appear below the proper name and dosage form. For example:

Armlupeg

(pegfilgrastim-xxxx) Injection

6 mg/0.6 mL

2. The route of administration is not specifically stated on the principal display panel. The route of administration is critical information that should appear on the principal display panel according to FDA draft guidance[f]. Include the route of administration on the principal display panel.
3. The principal display panel does not bear a declaration of the net quantity of contents. The net quantity statement is required per 21 CFR 201.51. We

[f] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

recommend you add a declaration of the net quantity of contents. For example, "1 x 0.6 mL single dose prefilled syringe."

C. Blister pack foil
    1. The blister pack foil is not labeled on the sample provided. Ensure the blister pack foil is labeled on the marketed product.
    2. As currently presented, the expiration date is absent. To minimize confusion and reduce the risk for deteriorated drug medication errors, add a placeholder for the expiration date and identify the format you intend to use. FDA recommends 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-MM-DD format if only numerical characters are used or 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.
    3. The strength does not contain a space between the numbers and unit of measure. We are concerned the lack of space between the numbers and unit of measure impairs readability. To improve readability, place adequate space between the numerical dose and unit of measure (e.g. 6 mg/0.6 mL instead of 6mg/0.6mL).

D. Container label
    1. Based on our review of the product sample we note the print is difficult to read against the clear background of the syringe and small font size. The color contrast of the (b) (4) text on the clear background appears difficult to read. Low contrast is a common cause of unreadable text. Therefore, we recommend revising the background (i.e. (b) (4) background) to improve the contrast and readability of the label.
    2. The strength does not contain a space between the numbers and unit of measure. We are concerned the lack of space between the numbers and unit of measure impairs readability. To improve readability, place adequate space between the numerical dose and unit of measure (e.g. 6 mg/0.6 mL instead of 6mg/0.6mL).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Armlupeg received on April 2, 2021 and May 24, 2021 from Lupin Limited (Biotech Division), and US-licensed Neulasta.

Table 2. Relevant Product Information for Armlupeg and US-licensed Neulasta		
Product Name	Armlupeg	US-licensed Neulasta [g]
Initial Approval Date	N/A	January 31, 2002
Proper Name	pegfilgrastim-xxxx	Pegfilgrastim
Indication	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Neulasta is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation.
Route of Administration	subcutaneous	Subcutaneous
Dosage Form	injection	Injection
Strength	6.0 mg/0.6 mL	6 mg/0.6 mL
Dose and Frequency	Patients with Cancer Receiving Myelosuppressive Chemotherapy: • 6 mg administered once per chemotherapy cycle. (b) (4) [redacted] • Do not administer Armlupeg between 14 days before and 24 hours after administration of cytotoxic chemotherapy.	Cancer patients receiving myelosuppressive chemotherapy: • 6 mg administered subcutaneously once per chemotherapy cycle. • For pediatric patients weighing less than 45 kg, refer to Table 1. • Do not administer Neulasta between 14 days before and 24 hours after cytotoxic chemotherapy. Patients with Hematopoietic Subsyndrome of Acute Radiation Syndrome:

[g] Neulasta [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 FEB 02. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125031s203lbl.pdf.

<table>
<tr>
<td></td>
<td>The Armlupeg prefilled syringe is not designed to allow for direct administration of doses less than0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Armlupeg less than 0.6 mL (6 mg) for direct administration to patients. (b) (4) [redacted] (b) (4) [redacted]</td>
<td>

Give 6 mg subcutaneously for adult victims with body weight≥ 45 kg for two doses given one week apart; for pediatric patients weighing less than 45 kg, use weight-based dosing.

The Neulasta prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Neulasta less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.

Table 1. Dosing of Neulasta for pediatric patients weighing less than 45 kg
<table>
<tr><th>Body weight</th><th>Neulasta Dose</th><th>Volume to administer</th></tr>
<tr><td>Less than 10kg*</td><td>See below*</td><td>See below*</td></tr>
<tr><td>10-20 kg</td><td>1.5 mg</td><td>0.15 mL</td></tr>
<tr><td>21-30 kg</td><td>2.5 mg</td><td>0.25 mL</td></tr>
<tr><td>31-44 kg</td><td>4 mg</td><td>0.4 mL</td></tr>
</table>
*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Neulasta
</td>
</tr>
<tr>
<td>How Supplied</td>
<td>Armlupeg (pegfilgrastim-xxxx) injection is a clear, colorless solution supplied in a prefilled single-dose syringe for manual use containing 6 mg Armlupeg, supplied with a 27-gauge, 1/2-inch</td>
<td>Neulasta is a clear, colorless, preservative-free solution available as single dose prefilled syringe with an UltraSafe® Needle Guard, containing 6 mg/0.6 mL of pegfilgrastim as well as an OnPro</td>
</tr>
</table>

	needle with an UltraSafe® Plus PassiveTM Needle Guard.	kit which contains 6 mg/0.6 mL solution in a single prefilled syringe co-packaged with the on-body Injector for Neulasta.
Storage	Store refrigerated between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.	Store refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 19, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Armlupeg' OR 'LUBT004'. Our search identified 1 previous review[h], and we considered our previous recommendations to see if they are applicable for this current review.

[h] DeGraw, S. Human Factors: Use-Related Risk Analysis Review for LUBT004* (pegfilgrastim-xxxx). IND 131463. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 28. RCM No.: 2020-999.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Armlupeg labels and labeling submitted by Lupin Limited (Biotech Division).

- Container label received on April 2, 2021
- Blister pack foil labeling received on April 2, 2021
- Shelf carton labeling received on April 2, 2021
- Instructions for Use (Image not shown) received on May 24, 2021, available from \\CDSESUB1\evsprod\bla761212\0004\m1\us\armlupeg-instructions-for-use.docx
- Prescribing Information and Patient Information (Image not shown) received on April 2, 2021, available from \\CDSESUB1\evsprod\bla761212\0001\m1\us\armlupeg-package-insert.docx

F.2 Label and Labeling Images

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

Container label – Syringe

Blister pack foil labeling

Shelf carton labeling

APPENDIX G. Pediatric Considerations

As part of Lupin Limited (Biotech Division)'s submissions to BLA 761212, Lupin Limited (Biotech Division) submitted a request for deferral for its pediatric assessments. We note the following:

- (b) (4)

- Order letter to sponsor of US-licensed Neulasta. On October 10, 2019, FDA issued an order letter pursuant to section 505B(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to the sponsor of US-licensed Neulasta, requiring it to submit pediatric assessments as described in section 505B(a)(2)(A) of the FD&C Act. As described in the letter, the sponsor of U.S.-licensed Neulasta is subject to a postmarketing requirement referred to as submission of pediatric assessments for Neulasta (pegfilgrastim) as described in section 505B(a)(2)(A) of the FD&C Act, including development of an "appropriate formulation" (presentation) that can be used to directly and accurately administer Neulasta (pegfilgrastim) to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg), and conducting any necessary human factors studies to evaluate the ability of healthcare providers and/or caregivers to measure the appropriate doses. In the letter, FDA stated it expected that a pediatric presentation – such as a vial or a pediatric-sized pre-filled syringe (with an appropriate concentration of product) – that can be used to directly and accurately deliver doses of less than 0.6 mL (6 mg) of pegfilgrastim to pediatric patients could be an "appropriate formulation" as described in section 505B(a)(2)(A). (FDA issued similar letters to sponsors of the licensed pegfilgrastim biosimilars, Udenyca (BLA 761039) and Fulphila (BLA 761075). On November 4, 2019, FDA licensed Ziextenzo (BLA 761045), which is also subject to a similar postmarketing requirement.)

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/s/

CELESTE A KARPOW
10/01/2021 12:37:38 PM

HINA S MEHTA
10/05/2021 09:48:04 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/4/2021

TO: Division of Non-Malignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761212

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in August 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: ANDA 213112.

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Accutest Research Labs	4th Floor, The Grand Monarch, Near Seema Hall, Anandnagar Road, Ahmedabad, Gujarat, India

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES J LUMALCURI
08/04/2021 11:45:15 AM