CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761134Orig1s000

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)

Date of This Memorandum:	October 4, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761134
Product Name, Dosage Form, and Strength:	Ryzneuta (efbemalenograstim alfa-vuxw) injection, 20 mg/mL
Applicant/Sponsor Name:	Evive Biotechnology (Singapore) PTE. LTD. (Evive)
TTT ID #:	2021-668-3
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised tray lid label received on October 3, 2023 for Ryzneuta. We reviewed the revised tray lid label for Ryzneuta (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Black, S. Label and Labeling Review for Ryzneuta (BLA 761134). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 SEP 29. TTT ID No.: 2021-668-2.

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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)

Date of This Memorandum:	September 29, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761134
Product Name, Dosage Form, and Strength:	Ryzneuta (efbemalenograstim alfa-vuxw) injection, 20 mg/mL
Applicant/Sponsor Name:	Evive Biotechnology (Singapore) PTE. LTD. (Evive)
TTT ID #:	2021-668-2
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised tray lid label and carton labeling received on September 28, 2023 for Ryzneuta. We reviewed the revised tray lid label and carton labeling for Ryzneuta (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.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations. We note that the net quantity statement on the tray lid label is separated on two different lines impacting readability; therefore, the revised tray lid label is unacceptable from medication error perspective. We provide our recommendation for the Applicant in Section 3.

3 RECOMMENDATIONS FOR EVIVE BIOTECHNOLOGY (SINGAPORE) PTE. LTD.

[a] Black, S. Label and Labeling Review for Ryzneuta (BLA 761134). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 SEP 27. TTT ID No.: 2021-668-1.

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

A. Tray Lid Label
    a. As currently presented, the net quantity statement is separated on two different lines impacting the readability of this statement. For readability, we recommend having "One Single-Dose Prefilled Syringe" all in one line underneath the statement "Recombinant…culture".

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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)

Date of This Memorandum:	September 27, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761134
Product Name, Dosage Form, and Strength:	Ryzneuta (efbemalenograstim alfa-vuxw)[a] injection, 20 mg/mL
Applicant/Sponsor Name:	Evive Biotechnology (Singapore) PTE. LTD. (Evive)
TTT ID #:	2021-668-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, tray lid label and carton labeling received on September 5, 2023 for Ryzneuta. We reviewed the revised container label, tray lid label and carton labeling for Ryzneuta (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b] We note that the Applicant confirmed the MM in the expiration date is numeric. In addition, we note, the Division decided to (b) (4) include concise, important administration information in the Prescribing Information[c]. Upon further review, we agree with this approach as the proposed

[a] The nonproprietary name, efbemalenograstim alfa-vuxw, was found conditionally acceptable on January 06, 2022.
[b] Black, S. Label and Labeling Memo for Ryzneuta (BLA 761134). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 AUG 18. TTT ID No.: 2021-668-1.
[c] Karpow, C. Label and Labeling Review for Ryzneuta (BLA 761134). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 12. OSE RCM No.: 2021-668.

prefilled syringe will be administered by healthcare professionals only and does not carry any new or unique risks.

2 CONCLUSION

The Applicant implemented most of our recommendations. In addition, Evive further revised the labels and labeling as follows:

- The trademark (b) (4) has been updated to registered trademark ®. (container label, tray lid label and carton labeling)
- The orientation of syringe image was reversed to match with the orientation of the actual syringe. (carton labeling and tray lid label)
- The font color of the strength statement was changed from (b) (4) to black. (carton labeling and tray lid label)
- The direction of the peel back redesigned to align with the packaging process and to ensure that the needle orientation matched with the carton. Along these lines, the strength statement and syringe image were relocated from the left to the right side. (tray lid label)

The revised container label, tray lid label and carton labeling are unacceptable from a medication error perspective for the following reasons:

- The strength statement lacks prominence. (tray lid label and carton labeling)
- The net quantity statement appears more prominent than the route of administration statement. (tray lid label)
- The Applicant did not relocate the route of administration "For Subcutaneous Use Only" statement to directly underneath the dosage form statement "Injection" but rather to directly underneath the syringe content statement. In addition, the route of administration statement was revised to "For Subcutaneous Injection by a Healthcare Provider Only ". (tray lid label)
- The Applicant removed (b) (4) from the trademark logo, reduced the size of the logo and changed the font color (b) (4) to black; however, the logo is still too prominent and competes with important information on the principal display panel (PDP). (tray lid label and carton labeling).

We provide additional recommendations for the Applicant in Section 3.

3 RECOMMENDATIONS FOR EVIVE BIOTECHNOLOGY (SINGAPORE) PTE. LTD.

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

A. Tray Lid Label
    a. The strength statement lacks prominence. Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that

prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement, NDC code, etc.). For example, relocate the strength statement in the orange box to directly underneath the dosage form as follows. To allow room for this change, relocate the manufacturer and license number information to another panel.

Ryzneuta
(efbemalenograstim alfa-vuxw)
Injection
20 mg/mL

b. We note in your response the route of administration statement was moved directly underneath the dosage form statement on the PDP; however, it was not revised on tray lid label submitted. Revise the route of administration statement to "For Subcutaneous Use Only" and relocate it directly underneath the dosage form and strength statement on the principal display panel (PDP) as follows. To allow room for this change, relocate the dosage statement "Dosage: See Prescribing Information" to the where the route of administration statement was.

Ryzneuta
(efbemalenograstim alfa-vuxw)
Injection
20 mg/mL
For Subcutaneous Use Only

c. As currently presented, the net quantity statement appears more prominent than the route of administration statement. Lack of prominence of the route of administration statement may lead to administration errors. We recommend decreasing prominence of the net quantity statement through debolding the "One Single-Dose Prefilled Syringe" so it does not compete in prominence with the route of administration statement.

d. We note that (b) (4) was removed from the manufacturer logo and the size of the manufacturer logo/name was reduced; however, the manufacturer logo/name still competes in prominence with critical product information. Critical product information such as the proprietary name, nonproprietary name, and product strength should appear as the most prominent information on the PDP in accordance with 21 CFR 201.15. We continue to recommend decreasing the size of the manufacturer information so it does not compete with the prominence of important product information on the PDP.

B. Carton Labeling

a. The strength statement lacks prominence. Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement, NDC code, etc.). For example, relocate the strength statement in the orange box to directly underneath the dosage form as follows. To allow for this change, consider relocating the dosage and sterile solution statements to another panel.

Ryzneuta
(efbemalenograstim alfa-vuxw)
Injection
20 mg/mL

b. We note that (b) (4) was removed from the manufacturer logo and the size of the manufacturer logo/name was reduced; however, the manufacturer logo/name still competes in prominence with critical product information. Critical product information such as the proprietary name, nonproprietary name, and product strength should appear as the most prominent information on the PDP in accordance with 21 CFR 201.15. We continue to recommend decreasing the size of the manufacturer information so it does not compete with the prominence of important product information on the PDP.

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CLINICAL INSPECTION SUMMARY

Date	August 24, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Donna A. Whyte-Stewart, M.D., Sc.M., Medical Officer Ann Farrell, M.D., Director Maureen DeMar, M.P.H., Regulatory Project Manager Division of Nonmalignant Hematology (DNH) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
BLA	761134
Applicant	Evive Technology Singapore PTE. Ltd.
Drug	Efbemalenograstim alpha
NME	Yes
Division Classification	Anti-neutropenia therapeutic biologic agent
Proposed Indication	Reduction in 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.
Consultation Request Date	April 29, 2021
Review Type	Priority
Summary Goal Date	September 9, 2021
Action Goal Date	March 30, 2022
PDUFA Date	March 30, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical data from two Phase 3 studies GC-627-04 and GC-627-05, were submitted to the Agency in support of a Biologics License Application 761134 for efbemalenograstim alpha indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies. The Sponsor (Evive Technology Singapore PTE. Ltd.) inspection was requested by the Division of Nonmalignant Hematology (DNH) for its monitoring and oversight of Studies GC-627-04 and GC-627-05. Due to the COVID-19 pandemic, FDA conducted a remote regulatory assessment as an alternative to the onsite inspection. During the FDA audit, video conferencing via Zoom was conducted, and document sharing via an online platform (box.com) was deployed.

Based on the remote regulatory assessment, the sponsor’s monitoring and oversight appeared

adequate for Study GC-627-04 and Study GC-627-05.

II. BACKGROUND

Efbemalenograstim, F-627, is a recombinant fusion protein consisting of human granulocyte colony stimulating factor (G-CSF) and human immunoglobulin (Ig)G2 Fc fragments. For cyclophosphamide-induced neutropenia in monkeys, sponsor claims that efbemalenograstim, F-627, generated faster neutrophil recovery and reduced the severity of neutropenia.

The Sponsor submits this BLA for the following proposed indication: efbemalenograstim is a leukocyte growth factor indicated 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.

For this BLA under the PDUFA program review, Study GC-627-04 and Study GC-627-05 were part of the FDA submission for which a sponsor site inspection was sought by the OND clinical review division DNH.

Study GC-627-04

Study GC-627-04 was a Phase III, global, multi-center, randomized, double-blinded placebo-controlled clinical study which randomized subjects with Stage II to IV breast cancer in the adjuvant or metastatic setting who were to receive myelotoxic Taxotere® + Adriamycin (TA) chemotherapy treatment (docetaxel + doxorubicin, 75 and 60 mg/m^2, respectively). Subjects may have been scheduled for more than four cycles of chemotherapy; however, study participation was limited to a subject's first four cycles. The objective of the study was to evaluate the efficacy and safety of F-627 given as a single 20 mg fixed dose pre-filled syringe in the subject's first chemotherapy cycle in comparison to placebo.

The primary efficacy endpoint was the duration of Grade 4 (severe) neutropenia (ANC $<0.5 \times 10^9$/L) observed in chemotherapy Cycle 1.

This was a multicenter study. A total of 122 subjects were randomized, all were analyzed for efficacy and safety. The first subject's informed consent date was August 17, 2016. The last subject's last visit or contact date was November 28, 2017.

Study GC-627-05

Study GC-627-05 was a Phase III, multicenter, randomized, open-label, two-arm, active-controlled study which randomized female subjects (approximately 200 subjects per arm) with Stage I to III invasive breast cancer who were receiving neoadjuvant or adjuvant myelotoxic taxane + cyclophosphamide (TC; 75 mg/m^2 docetaxel + 600 mg/m^2 cyclophosphamide) chemotherapy treatment. Subjects may have been scheduled for more than four cycles of chemotherapy; however, study participation was limited to a subject's first four cycles. The primary objective of this study was to evaluate the efficacy of F-627 given as a single fixed dose (20 mg) pre-filled syringe as compared to Neulasta® standard dosing (6 mg) in the first chemotherapy cycle. The safety objective was to assess safety in subjects treated with the fixed dose regimen of F-627.

The primary efficacy endpoint was the duration of Grade 4 (severe) neutropenia, defined as the number of days in which the subject had an ANC $<0.5 \times 10^9$/L during Cycle 1 of their chemotherapy treatment. (ANC) of less than 0.5×10^9/L.

This study randomized subjects at 41 sites. There were 393 study subjects who were analyzed for the primary efficacy analysis. The first subject's informed consent calendar date was on April 2, 2018. The last subject's last visit or contact was on March 5, 2020.

III. RESULTS

Evive Technology Singapore PTE. Ltd.
50 Beach Road
#32-05/08 Gateway West
Singapore, SG 189720

Inspection dates: June 2 to 14, 2021

The FDA conducted a remote regulatory assessment (RRA) as an alternative to the onsite inspection. This was the first inspection of Evive Technology (Singapore) PTE. Ltd.

This RRA covered Studies GC- 627-04 and GC-627-05, respectively, submitted to the Agency in support of BLA 761134. Video conferencing via Zoom was conducted, and document sharing via an online platform (box.com) was deployed. This RRA was performed in accordance with Compliance Program 7348.810 Sponsors, Contract Research Organizations and Monitors and the assignment instructions.

Records from Sites 100 and 131 in Study GC-627-04 and from Sites 108 and 701 in Study GC-627-05 were evaluated. The following records were evaluated: organizational charts, standard operating procedures, investigator selection, monitoring plans, transfer of responsibilities, FDA 1572s, financial disclosure forms, subject protection and ethical oversite, safety plans, data management and investigational product accountability records.

FDA also interviewed study personnel and reviewed regulatory files, source records, including subject selection, randomization, and blinding activities of four enrolled subjects, adverse events, IP accountability and efficacy endpoints.

Despite the limited scope due to the logistical constraints of information exchange between the FDA and sponsor, the FDA assessment found that these sites were monitored throughout the studies, and clinical investigators carried out their responsibilities according to the FDA regulatory requirements.

In general, no significant deficiencies were observed during this remote regulatory assessment of the two studies in BLA 761134.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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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:	August 21, 2023
To:	Rolanda K. Bailey Regulatory Project Manager **Division of Nonmalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jina Kwak, PharmD Team Leader **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (nonproprietary):	[F-627] RYZNEUTA (efbemalenograstim alfa-vuxw)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761134
Applicant:	Evive Biotechnology Singapore PTE Ltd., Roberta Smithey, Authorized U.S. Representative

1 INTRODUCTION

On March 30, 2021, Evive Biotechnology Singapore PTE Ltd., Roberta Smithey, Authorized U.S. Representative, submitted for the Agency's review an original Biologics License Application (BLA) 761134 for [F-627] RYZNEUTA (efbemalenograstim alfa-vuxw) injection. The proposed indication for [F-627] RYZNEUTA (efbemalenograstim alfa-vuxw) injection is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignanices receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. We note that the proposed tradename RYZNEUTA was found conditionally acceptable on June 9, 2021 and the nonproprietary name suffix "-vuxw" was found conditionally acceptable on January 6, 2022 by the Division of Medication Error Prevention and Analysis (DMEPA).

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 April 13, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for [F-627] RYZNEUTA (efbemalenograstim alpha-vuxw) injection.

2 MATERIAL REVIEWED

- Draft [F-627] RYZNEUTA (efbemalenograstim alpha-vuxw) injection PPI received on March 30, 2021, and revised on May 13, 2021, and received by DMPP and OPDP on August 14, 2023.
- Draft [F-627] RYZNEUTA (efbemalenograstim alpha-vuxw) injection Prescribing Information (PI) received on March 30, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on August 14, 2023.
- Approved NEUPOGEN (filgrastim) injection comparator labeling dated April 18, 2023.
- Approved NEULASTA (pegfilgrastim) injection comparator labeling dated June 2, 2022 and 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.

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.

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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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)

Date of This Memorandum:	August 18, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761134
Product Name, Dosage Form, and Strength:	Ryzneuta (efbemalenograstim alfa- vuxw)[a] injection, 20 mg/mL
Applicant/Sponsor Name:	Evive Biotechnology (Singapore) PTE. LTD. (Evive)
TTT ID #:	2021-668-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, carton labeling and tray lid labeling received on December 16, 2021 for Ryzneuta. We reviewed the revised container label, carton labeling and tray lid labeling for Ryzneuta (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] In addition, we reviewed the prescribing

[a] The nonproprietary name, efbemalenograstim alfa-vuxw, was found conditionally acceptable on January 06, 2022.
[b] Karpow, C. Label and Labeling Review for Ryzneuta (BLA 761134). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 12. OSE RCM No.: 2021-668. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061d77b

information (PI)[c], patient information (PPI)[d] [redacted] received on May 13, 2021 to determine if they are acceptable from a medication error perspective.

2 BACKGROUND

On March 3, 2021, Evive submitted 351(a) BLA 761134 seeking licensure for Ryzneuta (efbemalenograstim alfa-vuxw) to be administered by healthcare providers only. DMEPA completed a label and labeling review for this application on October 12, 2021[f]. As part of our review and in conjunction with Office of Biotechnology Products (OBP), we communicated recommendations for container label, carton labeling and tray lid labeling to the Applicant on October 7, 2021[g]. In response, on October 20, 2021, Evive submitted revised container label, carton labeling and tray lid labeling. On December 9, 2021[h], in conjunction with OBP, we communicated additional recommendations for container label, carton labeling and tray lid labeling to the Applicant.

As the Agency was unable to conduct inspection of the Evive Biotechnology manufacturing facility due to COVID travel restrictions at that time, the initial goal date of March 30, 2022 was not met. Once Washington Open Public Meetings Act (OPMA) resumed foreign inspections, the Agency was able to conduct an inspection of the facility from May 30, 2023 to June 7, 2023. Therefore, the review process was resumed on July 11, 2023 with a tentative new goal date of October 13, 2023.

3 CONCLUSION

The Applicant implemented most of our recommendations for the container label, carton labeling and tray lid labeling from our last review dated October 12, 2021 and communicated via email on October 7, 2021 and December 9, 2021. We find the revised container label, carton

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[c] United-states-prescribing-information-tracked (BLA 761134 and Ryzneuta) Singapore (SG): Evive Biotechnology (Singapore) PTE. LTD; 2021 MAY 13. Available from: \\CDSESUB1\EVSPROD\bla761134\0008\m1\us\114-labeling\114a-draft-label\united-states-prescribing-information-tracked.docx

[d] Patient-information-leaflet-tracked (BLA 761134 and Ryzneuta) Singapore (SG): Evive Biotechnology (Singapore) PTE. LTD; 2021 MAY 13. Available from: \\CDSESUB1\EVSPROD\bla761134\0008\m1\us\114-labeling\114a-draft-label\patient-information-leaflet-tracked.docx

[e] [redacted] (BLA 761134 and Ryzneuta) Singapore (SG): Evive Biotechnology (Singapore) PTE. LTD; 2021 MAY 13. Available from: \\CDSESUB1\EVSPROD\bla761134\0008\m1\us\114-labeling\114a-draft-label\[redacted]

[f] Karpow, C. Label and Labeling Review for Ryzneuta (BLA 761134). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 12. OSE RCM No.: 2021-668. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061d77b

[g] DeMar, M. FDA Communication: BLA 761134 Carton and Container Information Request (IR) for Ryzneuta. Silver Spring (MD): FDA, CDER, DNH (US); 2021 OCT 07. BLA 761134. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061beec and https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061c29c

[h] DeMar, M. FDA Communication: BLA 761134 DMEPA and OBP Carton and Container IR for Ryzneuta. Silver Spring (MD): FDA, CDER, DNH (US); 2021 DEC 09. BLA 761134. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80630d72

labeling and tray lid labeling unacceptable from a medication error perspective due to the following:

- General: nonproprietary name suffix is missing
- Container Label: strength lacks prominence and product code in close proximity to expiration date
- Tray Lid: route of administration lacks prominence, net quantity is missing, redundant vial content statement, manufacturer information is too prominent, storage statement is inconsistent with PI
- Carton Labeling: instructions to be administered by HCP is missing, redundant vial content statement, the package type term is not included in the net quantity statement, manufacturer information is too prominent, storage statement is inconsistent with PI, and the 2-letter abbreviation in the expiration date is not defined.

In addition, upon review of the prescribing information (PI) and patient information (PPI), we find the PI unacceptable as the storage statement is inconsistent with the storage statement on the carton labeling and container label. We find the PPI acceptable and do not have additional recommendations. Upon review (b) (4) we find (b) (4) unacceptable (b) (4) Therefore, we provide our recommendations for the PI (b) (4) to the Division in Section 4.

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

A. Prescribing Information

1. Section 16 How Supplied/Storage and Handling
    a. As currently presented, the storage statement is not consistent with the carton labeling and container labels. We recommend revising to "Store refrigerated at 2° to 8°C (36° to 46°F) in the carton to protect from light."

B. (b) (4)

(b) (4)

[redacted]

5 RECOMMENDATIONS FOR EVIVE BIOTECHNOLOGY (SINGAPORE) PTE. LTD.

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

A. General Comments (Container labels, Carton Labeling, and Tray lid labeling)
    1. As currently presented, the suffix is missing from the nonproprietary name on the principal display panel (PDP). A distinguishable nonproprietary name will facilitate accurate identification of the biological product by healthcare providers and patients. Please refer to the General Advice Letter issued on January 11, 2022 which notified you of the nonproprietary name suffix found conditionally acceptable for your proposed product. Should your BLA be approved during this review cycle, efbemalenograstim alfa-vuxw will be the proper name designated in the license. Revise the nonproprietary name on all labels and labeling to incorporate the FDA-designated nonproprietary name suffix, -vuxw, appended to the core name, efbemalenograstim alfa so that the proper name appears as efbemalenograstim alfa-vuxw throughout the labels and labeling.

B. Container Label
    1. The strength statement lacks prominence. Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Increase the prominence of the strength statement by colored box similar to the method used on the tray label and carton labeling in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement, NDC code, etc.). In addition, to increase the prominence of the strength statement, relocate the statement “Single-Dose Prefilled Syringe” to directly underneath the route of administration statement.
    2. As currently presented, the product code “301878” is located in close proximity to the expiration date. Numbers or codes located in close proximity to the expiration date may be mistaken as the expiration date. We recommend you

ensure that there are no other numbers located in close proximity to the expiration date.

C. Tray Lid Label

1. The route of administration appears less prominent on the principal display panel (PDP). Lack of prominence of the route of administration statement may lead to administration errors. For increased prominence, relocate the route of administration statement "For Subcutaneous Use Only" directly underneath the dosage form statement on the PDP.
2. The net quantity statement does not appear on the PDP of the tray label. Failure to include the net quantity statement on the principal display panel may result in confusion regarding the contents of the tray label. We recommend including a net quantity statement (e.g., One Single-Dose Prefilled Syringe) on the PDP and ensure it is located away from and less prominent than the product strength, such as to the bottom of the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3. Remove the redundant statement (b) (4)
4. The manufacturer information (e.g., manufacturer name and logo) competes in prominence from critical product information (e.g., proprietary name, established name, strength). Critical product information such as the proprietary name, nonproprietary name, and product strength should appear as the most prominent information on the PDP in accordance with 21 CFR 201.15. Decrease the size of the manufacturer information so it does not compete with the prominence of important product information on the PDP.
5. As currently presented, the storage statement is not consistent with the PI. To ensure consistency with the PI, revise (b) (4) to "Store refrigerated at 2° to 8°C (36° to 46°F) in the carton to protect from light. Do Not Freeze or Shake."

D. Carton Labeling

1. The carton labeling does not contain instructions that this product must be administered by healthcare provider only. Failure to include instructions on the carton labeling may result in patients or caregivers administering the product, which may lead to medication errors. We recommend revising, (b) (4) (b) (4) to read "For Subcutaneous Injection by a Healthcare Provider Only" to help alert patients, caregivers, and healthcare providers (particularly pharmacies who may dispense the product directly to the patient) that the patient should take the product to their healthcare provider for administration.
2. Remove the redundant statement (b) (4)
3. As currently presented, the package type term, Single-Dose Prefilled Syringe, is not stated on the PDP of the carton labeling. Consistent use of the correct

package type term will promote proper use of the drug product. The lack of this information may lead to wrong technique medication errors during preparation of the product. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). Revise (b) (4) to "Contains One Single-Dose Prefilled Syringe." to include the package type term on the PDP.

4. The manufacturer information (e.g., manufacturer name and logo) competes in prominence from critical product information (e.g., proprietary name, established name, strength). Critical product information such as the proprietary name, nonproprietary name, and product strength should appear as the most prominent information on the PDP in accordance with 21 CFR 201.15. Decrease the size of the manufacturer information so it does not compete with the prominence of important product information on the PDP.
5. As currently presented, the storage statement is not consistent with the PI. To ensure consistency with the PI, revise (b) (4) to "Store refrigerated at 2° to 8°C (36° to 46°F) in the carton to protect from light. Do Not Freeze or Shake."
6. As currently presented, the expiration date includes a 2-letter abbreviation (e.g., YYYY-MM-DD). 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.

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/s/

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08/21/2023 04:06:49 PM

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

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

Memorandum

Date: August 17, 2023

To: Rolanda Bailey, Regulatory Project Manager
Division of Nonmalignant Hematology (DNH)

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

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

CC: Jina Kwak, PharmD, RAC, Team Leader
(OPDP)

Subject: **RYZNEUTA** (efbemalenograstim alfa-vuxw) injection, for subcutaneous use

BLA: 761134

Background:
In response to DNH's consult requests dated April 13, 2021, and August 14, 2023, OPDP has reviewed the proposed Prescribing Information (PI), (b) (4) (b) (4) Patient Package Insert (PPI), and carton and container labeling for the original BLA submission for **RYZNEUTA** (efbemalenograstim alfa-vuxw) injection, for subcutaneous use.

PI/ (b) (4)
OPDP's review of the proposed PI and (b) (4) are based on the draft labeling emailed to OPDP on August 14, 2023 and our comments are provided below.

PPI:
A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, 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 December 16, 2021, 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
08/17/2023 02:02:21 PM

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	8/10/2021		
To:			
Requesting Center/Office	CDER/OND	**Clinical Review Division**	N/A-OPQ/OSE led
From	Shanly Chen OPEQ/OHT3/DHT3C		
Through (Team)	Suzanne Hudak, Injection Devices Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	ICCR: 00726095 ICC: ICC2100527 Submission: BLA 761134 Sponsor: Evive Biotechnology Singapore Pte. Ltd. Drug/Biologic: Efbemalenograstim Indications for Use: Decrease in 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)**
Shanly M. Chen -S Shanly M. Chen -S 2022.03.31 17:50:14 -04'00'		Alan M. Stevens -S3

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

\\CDSESUB1\evsprod\bla761134\0008\m1\us\114-labeling\114a-draft-label\ (b) (4) .pdf
K123743

(b) (4)

The UltraSafe PLUS device are prefilled standard glass syringes assembled prefilled by the pharma customer. The PLUS device is composed of a guard, body, spring and plunger. The needle guard is a passive anti-needle stick device. It is classified as passive activation in that no other actions are required to engage the safety feature; one just needs to fully administer the injection. Upon completion of the injection, the syringe will retract and the guard locks over the needle. It is a tactile and/or visual recognition and/or audible recognition that the device safety feature has activated.

[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 and will not cover functions of the primary container (container content, 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 or self-administration
Injection Site	Thigh, abdomen
Injection tissue and depth of injection	SQ
Needle connection (e.g. luer, slip tip, staked)	Staked
Needle safety type (active or passive)	Active
Delivered Dose Volume	20mg/1mL
Shelf-life/Storage, including excursions (e.g., 36months, 5C)	3 years at 2C – 8C

3. DEVICE PERFORMANCE REVIEW

3.1. Design Verification & Validation

\\CDSESUB1\evsprod\bla761134\0023\m1\us\111-info-amend\response-to-information-request.pdf

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)	Y, N=500 97.5/99.5%, attribute, Y	Y, Human Factors testing K123743 / Original / Attachment 3, Y	25C – 6 months accelerated aging, Y	Simulated shipping per ASTM D4169, 20 PFS from 3 batches, 95/99, k = 2.90, Y	Y, 3 orientations with 1m free fall, n=60 Also did free fall test with only 1 orientation but n=299
Needle safety lockout force/override force/safe mode challenge		Y, N=500 97.5/99.5%, attribute	Y, anthropometric data		Force ≥ 80 after shipping, n=60, 95/99, k = 2.90	
Needle Safety Pre-activation		Y, N=500 97.5/99.5%, attribute	Y, HF testing K123743 / Original / Attachment 3			
Needle safety Access in safe mode		Y, See drawing below	Y, See drawing below	*N/A*	*N/A*	*N/A*

(b) (4)

Information Request #1 Sent	(b) (4)

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Information Request #1.4	(b) (4) [redacted]
Sponsor Response	\\CDSESUB1\evsprod\bla761134\0043\m1\us\111-info-amend\response-to-information-request.pdf
Reviewer Comments	Sponsor did additional testing (b) (4) [redacted] acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

4. CONTROL STRATEGY REVIEW

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

(b) (4) [redacted]

Reviewer Comments See table above

Information Request #2 Sent 8/12/2021	(b) (4) [redacted]
Sponsor Response	
Reviewer Comments	
Response Adequate:	☐ **Yes** ☐ **No, See IR #**

Information Request #2.2 Sent 8/31/21	(b) (4) [redacted]

Sponsor Response	(b) (4)
Reviewer Comments	Unacceptable see IR 2.3
Response Adequate:	☐ **Yes** ☐ **No, See IR #**

Information Request #2.3 Sent	(b) (4)
Sponsor Response	
Reviewer Comments	Sponsor has agreed (b) (4) test requirements by Catalent. Agree with sponsor that these EPR as unlikely to be affected during filling and control by both BD (who manufactures the syringe) and Catalent (who does final filling of syringe). Acceptable
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

<<END OF REVIEW>>

5. APPENDIX A (INFORMATION REQUESTS)

<<Complete Response Deficiencies should be listed on the cover page of the memo>>

5.1. 74 Day Letter

<<Only list the IRs here (clean version). Do not put your review of IRs in this section.>>

5.2. Midcycle/DRL Deficiencies

5.3. Information Requests (Post-Midcycle/DRL)

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/s/

ROLANDA K BAILEY
10/05/2023 05:18:18 PM
On behalf of Shanly Chen

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:	October 12, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	BLA 761134
Product Name, Dosage Form, and Strength:	Ryzneuta (efbemalenograstim alpha-xxxx)[a] injection, 20 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD.
FDA Received Date:	March 30, 2021 & May 13, 2021
OSE RCM #:	2021-668
DMEPA 2 Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

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

1 REASON FOR REVIEW

As part of the approval process for Ryzneuta (efbemalenograstim alpha-xxxx) injection, EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD. Submitted BLA 761134 for Agency review. This review evaluates the proposed Ryzneuta prescribing information (PI), patient information leaflet (PIL), [redacted] (b) (4) carton labeling, and container label for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Ryzneuta is being proposed to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs with a clinically significant incidence of febrile neutropenia. It is being proposed as a 20 mg/mL subcutaneous injection in a single-dose prefilled syringe (PFS). A Type C Written Response was provided to EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD on August 2, 2019[b]. EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD requested agency concurrence with their determination that a HF validation study of the F-627 PFS is not required. The Agency responded that since the proposed product is intended for healthcare provider use, human factors validation data is not required to be submitted for review as part of the marketing application.

2 MATERIALS REVIEWED

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

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

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

[b] Scott, Kimberly L. Meeting Request – Written Responses for F-627 (Recombinant Human G-CSF-Fc). Silver Spring (MD): FDA, CDER, OND DIVISION OR OSE (US); 2019 AUG 02. IND 112198.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), patient information leaflet (PIL), (b) (4) carton labeling, tray lid labeling, and container label for Ryzneuta to identify deficiencies that may lead to medication errors and other areas of improvement. The Type C Written Response dated August 2, 2019 indicates the proposed product is intended for healthcare provider use only. (b) (4) As such, we sent an Information Request (IR) on May 5, 2021 asking EVIVE Biotechnology to conduct a new use-related risk analysis as the product is being proposed for use by patients and caregivers. On May 13, 2021 EVIVE responded to the IR stating, "they intend to revise the USPI, PIL (b) (4) With this response, EVIVE submitted revised labeling (b) (4)

We note the proposed prefilled syringe will be administered by healthcare professionals only. In addition, the proposed prefilled syringe does not have any new or unique risks. As such we recommend (b) (4) include concise, important administration information in the PI as needed.

The proposed PI, container label, tray lid labeling, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide recommendations for the Division in Section 4.1 and recommendations for EVIVE in Section 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

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

A. General Comments for Prescribing Information (PI)
    1. The PI does not contain a nonproprietary name suffix placeholder, such as "xxxx." We recommend adding a nonproprietary name suffix placeholder throughout the PI. Once the nonproprietary name suffix is found conditionally acceptable, the placeholder should be replaced with the designated suffix.
    2. The strength is listed as, (b) (4) We recommend revising the strength presentation to, "20 mg/mL" for simplicity.

B. Highlights of Prescribing Information (HPI)
    1. The first bullet, (b) (4) (b) (4) is not needed (b) (4) We recommend removing this bullet from the Dosage and Administration section of the HPI.

C. Prescribing Information
    1. Dosage and Administration

a. We recommend including the statement "TRADENAME should be administered by a healthcare professional only." to ensure this important information is not missed.
b. We note the statement about the prefilled syringe not bearing graduation marks is absent. We recommend you add a statement similar to, "[TRADENAME] prefilled syringe does not bear graduation marks and is intended only to deliver the entire contents of the syringe (20 mg/mL) for direct administration to adult patients." to Section 2 Dosage and Administration.
c. We recommend adding a statement regarding the location of the injection and administration technique. For example, "Administer injection by pinching the skin and holding. Inject into the abdomen, the back or side of the upper arms, or the thighs. Rotate injection sites. An injection should never be given into scar tissue or areas that are reddened, inflamed, or swollen. If injecting into the abdomen, avoid a 2 in diameter circle around the navel.".
d. We recommend including a statement that informs users of the needle guard. We recommend adding "Once the entire dose has been injected, the needle safety device will be triggered, pulling the needle automatically from the skin and into the barrel.".

4.2 RECOMMENDATIONS FOR EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD.

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

A. General Comments (Container labels, Carton Labeling, and Tray lid labeling)

1. The labels and labeling do not contain a nonproprietary name suffix placeholder, such as "xxxx." We recommend adding a nonproprietary name suffix placeholder throughout the labels and labeling. Once the nonproprietary name suffix is found conditionally acceptable, the placeholder should be replaced with the designated suffix.

2. The strength presentation is not presented per total volume in the highlighted yellow box. We recommend revising the strength in the box to "20 mg/mL".

3. The term, [redacted] (b) (4) appears throughout the labels and labeling. We recommend you revise [redacted] (b) (4) to "Single Dose Prefilled Syringe" throughout the labels and labeling.

4. As currently presented, the placeholder, 'XXXX-XXXX-XX' appears for the NDC. We request you include your proposed NDC on labels and labeling.

B. Syringe Container Label

1. The finished dosage form "Injection" is not present on the label. Consider including the finished dosage formulation, "Injection", directly beneath the proper name on the principal display panel.

2. The route of administration is not present on the principal display panel (PDP). The route of administration is critical information that should be available to users at the time of product administration. Therefore, we recommend you add a statement similar to, "For Subcutaneous Use Only" to the PDP.
3. The NDC number is absent. We recommend you include the NDC number on your container label.
4. Ensure the font is legible against the syringe barrel. In most cases, (b) (4) Please confirm the background of the syringe container label.
5. The linear barcode is absent. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual container as required per 21 CFR 201.25(c)(2). Ensure the barcode is surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
6. The format of 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 forward slash or a hyphen be used to separate the portions of the expiration date.

C. Tray lid labeling
   1. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Dosage: See prescribing information."

D. Carton Labeling
   1. The statement, (b) (4) appears on the side panel. We are concerned this storage statement might be overlooked on the side panel alone. If space permits, we recommend you increase the prominence of this statement and consider moving it to the back panel in addition to the side panel.
   2. A 'Recommended Dosage' statement is absent. We recommend you include a statement that reads, "Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ryzneuta received on March 30, 2021 from EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD..

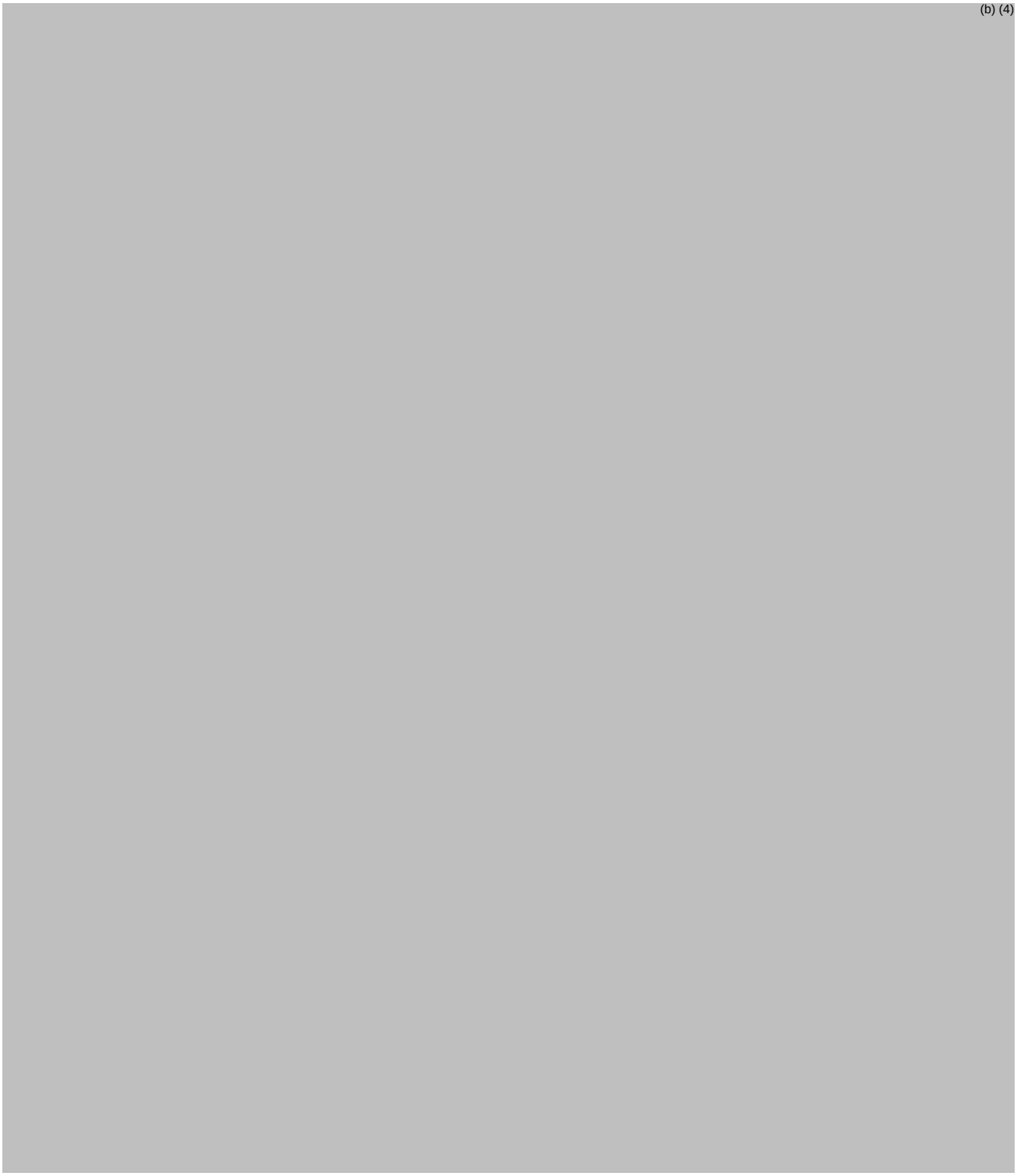
Table 2. Relevant Product Information for Ryzneuta	
Initial Approval Date	N/A
Nonproprietary Name	efbemalenograstim alpha-xxxx
Indication	to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
Route of Administration	Subcutaneous
Dosage Form	injection
Strength	20 mg/mL
Dose and Frequency	(b) (4)
How Supplied	supplied in a prefilled single-dose syringe with a 27-gauge, 1/2-inch needle and an UltraSafe Passive™ Needle Guard
Storage	Store refrigerated between 2°C to 8°C (36°F to 46°F) in the carton
Container Closure	The syringe consists of the following primary packaging components: 1. Syringe barrel, transparent glass ((b) (4) glass (b) (4)) with a stainless-steel hypodermic needle. 2. Needle shield, rubber formulation (b) (4) gray. 3. Rubber stopper, (b) (4) gray (b) (4) The secondary packaging components are: 1. Rigid shield (b) (4) 2. Plunger rod (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 27, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Ryzneuta' OR 'efbemalenograstim' OR 'F-627' OR 'IND 112198' OR 'BLA 761134'. Our search identified 0 previous reviews.

APPENDIX F. INFORMATION REQUESTS

On May 5, 2021, DMEPA sent the following information request (IR) to EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD.:



(b) (4)

On May 13, 2021, we received the following response from EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD.:

- Cover Letter: \\CDSESUB1\evsprod\bla761134\0008\m1\us\12-cover-letter\cover-letter-0008-13may2021-response-to-request.pdf
- Full Response: \\CDSESUB1\evsprod\bla761134\0008\m1\us\111-info-amend\response-to-information-request.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Ryzneuta labels and labeling submitted by EVIVE BIOTECHNOLOGY SINGAPORE PTE. LTD..

- Container label received on March 30, 2021
- Carton labeling received on March 30, 2021
- Tray lid labeling received March 30, 2021
- (b) (4) (Image not shown) received on March 30, 2021, available from \\CDSESUB1\evsprod\bla761134\0008\m1\us\114-labeling\114a-draft-label\i(b) (4).pdf
- Patient Information (Image not shown) received on March 30, 2021 available from \\CDSESUB1\evsprod\bla761134\0008\m1\us\114-labeling\114a-draft-label\patient-information-leaflet.pdf
- Prescribing Information (Image not shown) received on March 30, 2021, available from \\CDSESUB1\evsprod\bla761134\0008\m1\us\114-labeling\114a-draft-label\united-states-prescribing-information.docx

G.2 Label and Labeling Images

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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/

CELESTE A KARPOW
10/12/2021 03:44:54 PM

HINA S MEHTA
10/13/2021 02:27:39 PM